FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

Ninety-fourth Meeting

Tuesday,
January 12, 1999

Main Conference Room
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, Maryland

FREILICHER & ASSOCIATES, COURT REPORTERS
14003 Briston Street, Suite F
Laurel, Maryland 20707
(301) 881-8132

IN ATTENDANCE:

Voting Members

JAMES P. McCULLEY, M.D., Chair
MARK A. BULLIMORE, MCOptom, Ph.D.
EVE J. HIGGINBOTHAM, M.D.
JANICE M. JURKUS, O.D.
MARIAN S. MACSAI, M.D.
JOSE S. PULIDO, M.D.
JOEL SUGAR, M.D.

Consultants, Deputized to Vote

KAREN BANDEEN-ROCHE, Ph.D.
MICHAEL R. GRIMMETT, M.D.
ALICE Y. MATOBA, M.D.
WOODFORD S. VAN METER, M.D.
MING X. WANG, M.D., Ph.D.

Non-Voting Members

RENEE A. MIDDLETON, Ph.D., Consumer Representative
MARCIA S. YAROSS, Ph.D., Industry Representative

Panel Executive Secretary

SARA M. THORNTON

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (8:09 a.m.)

DR. McCULLEY: I'd like to call to order the 94th meeting of the Ophthalmic Devices Panel.

I would like to turn the floor now to Sara Thornton for introductory remarks.

MS. THORNTON: Good morning. I'd like to welcome you all to the meeting. I'm Sara Thornton, the executive secretary for the Ophthalmic Devices Panel. Before we proceed with today's agenda, there are a few announcements I'd like to make.

I'd like to remind everyone that you're requested to sign in on the attendance sheets in the registration area just outside this meeting room. You may pick up an agenda and information about today's meeting and how to obtain summary minutes or panel transcripts there as well.

You should make a note that the panel meeting tentatively scheduled for March 11th and 12th of this year has been canceled. The status of the May 3 and 4 meeting will be available early in March. Check our Web site or you can call me. It should be on the hotline, though, and we'll let you know as soon as we know.

Messages for the panel members and FDA participants, information and special needs should be directed through Ms. Ann-Marie Williams or Ms. Shirley

Meeks who are available at the registration table or in the registration area. The phone number for contacting you here is (301) 443-8011. For those of you with cell phones and pagers, we ask that you turn them off or put them on vibration mode while you are in this room.

Your lunch sheets, which I hope all of you have had an opportunity to fill out and submit the required monies to Ms. Williams, I hope you've done that now, but if you haven't, would you finish that business up at the break, please, so we can get those orders over and you'll have your lunch when you have the time to eat it.

Lastly, will all meeting participants please speak into the microphone and give your name clearly so that the transcriber will have an accurate recording of your comments.

At t his time, I'd like to introduce our panel to you. We are missing at the moment a couple of folks and I will introduce them when they come in. But I would like to begin the introductions. I think it would be good to start with Dr. McCulley here to my right.

DR. McCULLEY: Jim McCulley, professor and chairman, Department of Ophthalmology, University of Texas Southwestern Medical School in Dallas.

DR. HIGGINBOTHAM: Eve Higginbotham, professor and chair, Department of Ophthalmology, University of

Maryland, Baltimore.

DR. SUGAR: Joel Sugar, professor of ophthalmology, University of Illinois at Chicago.

DR. BULLIMORE: Mark Bullimore, the Ohio State University College of Optometry.

DR. JURKUS: Jan Jurkus, professor, Illinois College of Optometry in Chicago.

DR. ROSENTHAL: Ralph Rosenthal, director, Division of Ophthalmic Devices.

DR. YAROSS: Marcia Yaross, director of regulatory affairs, Allergan, and industry representative to the panel.

DR. BANDEEN-ROCHE: Karen Bandeen-Roche, associate professor of biostatistics, Johns Hopkins University, Baltimore.

DR. GRIMMETT: Michael Grimmett, assistant professor of clinical ophthalmology, University of Miami School of Medicine, Bascom Palmer Eye Institute.

DR. WANG: Ming Wang, assistant professor of ophthalmology, Vanderbilt University.

DR. VAN METER: Woodford Van Meter, private practice, cornea and external disease, Lexington, Kentucky.

DR. MATOBA: Alice Matoba, associate professor of ophthalmology, Baylor College of Medicine, Houston, Texas.

DR. MACSAI: Marian Macsai, professor of ophthalmology, West Virginia University School of Medicine.

MS. THORNTON: Thank you, and welcome to you all.

I would like to point out a typo in the first page of the agenda. My sincerest regrets to Dr. McCulley. He is the Chair. He is not the Interim Chair.

DR. McCULLEY: As you pointed out, I'm still in training.

MS. THORNTON: Yes.

DR. McCULLEY: As I pointed out, I'll be in training the day I leave.

MS. THORNTON: Now I think I can turn it back over to Dr. McCulley, and we will proceed with the first portion of our meeting.

DR. McCULLEY: I'd like to open the public hearing session of this meeting. We had only one person who indicated he wished to speak before who has canceled. If there is anyone in the audience who would like to come to the podium to make comments, you're welcome to do so.

(No response.)

DR. McCULLEY: Seeing none, that closes the open public hearing.

There will be an opportunity for public comments toward the end of the deliberations of the PMA and

prior to the panel vote. That comment period will be for comments relative specifically to the PMA and deliberations that have taken place.

We'll now begin the open committee discussion. I'll turn the floor back to Ms. Thornton.

MS. THORNTON: First, I'd like to read the conflict of interest statement for the Ophthalmic Devices Panel meeting of January 12, 1999. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

"To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the government.

"We would like to note for the record that the Agency took into consideration certain matters regarding Drs. Janice Jurkus, James McCulley, and Ming Wang. These panelists reported past and/or current involvement in firms

at issue but in matters not related to today's agenda. Since their interests are unrelated, the Agency has determined that they may participate in the committee's deliberations.

"In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participant should excuse himself or herself from such involvement and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon."

I would like now to read the appointment to temporary voting status. "Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, as amended April 20, 1995, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for the duration of this meeting on January 12, 1999: Dr. Karen Bandeen-Roche, Dr. Michael R. Grimmett, Dr. Woodford S. Van Meter, Dr. Alice Y. Matoba, Dr. Ming X. Wang.

"For the record, these persons are special government employees and are consultants to this panel or

consultants or voting members of another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting." Signed, Dr. D. Bruce Burlington, Director of the Center for Devices and Radiological Health, dated December 15, 1998.

Thank you.

DR. McCULLEY: Okay. We will shortly begin the division updates. But prior to that in just a moment, Ms. Thornton has another announcement to make. When we begin that, we will begin with Dr. Rosenthal. But prior to that, Sally?

MS. THORNTON: Yes, I would just like to announce for the record that Dr. Pulido and our consumer representative, Dr. Renee Middleton, are not here and will not be here for this meeting, and their absences were not anticipated.

Thank you.

DR. McCULLEY: Dr. Rosenthal?

DR. ROSENTHAL: I have no comments, Mr. Chairman.

DR. McCULLEY: Branch updates. Dr. Saviola?

DR. SAVIOLA: Good morning. I have one update to report to the panel. Our branch has completed a review of the Wesley-Jessen Precision UV (Vasurfilcon A) soft

contact lens that requested a modification to the labeling to include an additional indication statement, and a modified UV lens labeling note and warning statement.

Since the lens is marketed for both daily wear and extended wear, a 510k, K982988, and a PMA supplement, P940013/S006, were both reviewed and cleared for marketing as of last week.

The additional indication statement reads as follows. It's a single sentence. "Precision UV lenses help protect against transmission of harmful UV radiation to the cornea and into the eye." The remainder of the indication statement was unchanged.

The revised warning is: "UV-absorbing contact lenses are not substitutes for protective UV-absorbing eyewear such as UV-absorbing goggles or sunglasses because they do not completely cover the eye and surrounding area. You should continue to use UV-absorbing eyewear as directed."

The new phrase in the warning, "because they do not completely cover the eye and surrounding area," was added to explain the limitations of the lens.

The new note and the old note are on the overhead and I will read them for the record. The new note reads: "Long-term exposure to UV radiation is one of the risk factors associated with cataracts. Exposure is based

on a number of factors such as environmental conditions -- altitude, geography, cloud cover -- and personal factors -- extent and nature of outdoor activities. UV-absorbing contact lenses help provide protection against harmful UV radiation. However, clinical studies have not been done to demonstrate that wearing UV-absorbing contact lenses reduces the risk of developing cataracts or other eye disorders. Consult your eyecare practitioner for more information."

Previously, the note had stated: "The effectiveness of wearing UV-absorbing contact lenses in preventing or reducing the incidence of ocular disorders associated with exposure to UV-light has not been established at this time."

During the review of these documents, the recommendation of the Promotion and Advertising Staff in the Office of Compliance were sought and considered by our branch. Also, since the note, warning, and indications appear in patient labeling, a review of the proposed changes was conducted by human factors reviewers in the Office of Surveillance and Biometrics, Division of Device User Programs.

This was a literature-based application. There have been a number of studies published since the original policy letter was issued in 1987. However, since there are

no clinical data to support the claim that a UV-absorbing lens will reduce the incidence of cataracts, that statement is not included in the revised labeling.

We are currently working on a policy to advise other firms how they may proceed to change their product labeling for other UV-absorbing contact lenses and we will be issuing guidance to the industry in the near future. Our goal is to take the least burdensome regulatory path. However, any modification to a currently approved indication statement would require submission of a new 510k and/or PMA supplement, depending on the lens' indication of daily or extended wear.

That concludes my update.

DR. McCULLEY: Thank you. I should have pointed out that Dr. Saviola is chief of the Vitreoretinal and Extraocular Devices Branch.

Now I would like to recognize Dr. Morris Waxler, chief, Diagnostic and Surgical Devices Branch.

DR. WAXLER: Good morning. I want to thank the staff of the Diagnostic and Surgical Devices Branch, the medical officers, and others in the Division of Ophthalmic Devices without whose diligent work device applications would not be approved. Thanks also to panel members who have been helpful on many occasions.

On December 17, 1998 the Food and Drug

Administration approved PMA P970053 for the Nidek EC-5000 Excimer Laser System for PRK treatment for the reduction or elimination of mild to moderate myopia, -0.75 to -13.00 diopter spherical equivalent, less than or equal to 0.75 diopter astigmatism.

The FDA has approved a number of sponsor-investigator clinical trials to investigate a wide range of important variables in the PRK and LASIK treatment of myopia and hyperopia, with and without astigmatism. These studies are, or have been, conducted using refractive lasers from many of the manufacturers. A large amount of information has been learned about PRK and LASIK. Many of the recent applications from sponsor-investigators are redundant and therefore have been disapproved. The Agency will approve additional sponsor-investigator clinical trials for excimer lasers only if the sponsor has submitted a study that has a unique and scientifically sound investigational plan.

Thanks.

DR. McCULLEY: Does that conclude your report?

DR. WAXLER: Yes.

DR. McCULLEY: Thank you.

Next, Donna Lochner, chief, Intraocular and Corneal Implants Branch.

MS. LOCHNER: Thank you. First, I'm pleased to

announce that Staar Surgical Company's PMA P880091/Supplement 14 for their Toric Intraocular Lens was approved by the FDA on November 4th of 1998. This PMA was reviewed by the panel in July of 1998.

Second, I'd like to make the panel aware that the Division plans to release in the very near future a guidance document entitled "Accountability Analysis for Clinical Studies for Ophthalmic Devices." This document will be available shortly on FDA's Web site and will be mailed to the panel when it is released. The guidance is intended to provide general information about the analysis of accountability in ophthalmic device investigational and marketing applications and notifications. The guidance defines common terms used in reporting accountability, describes in a fair amount of detail the key factors to consider in presenting loss to follow-up analyses, and provides suggested formats for reporting accountability.

The Division hopes terminology and methods of presentation can be somewhat standardized so that the Division, sponsors, and the panel can more effectively analyze these data and so that a common understanding of accountability may result. We will appreciate any comments you may have when the document is released.

Third, the Intraocular and Corneal Implants Branch also plans to release very shortly the next draft of

the intraocular lens guidance document. Of particular note in the release of this draft version is that it contains an update of the historical control, or FDA grid, clinical data. Again, we plan to mail a copy to the panel when it becomes available, and we will welcome any comments you may have on any part of the guidance.

And fourth and last, I'd like the panel and public to be aware that FDA has issued a requirement that all medical devices or packaging containing natural rubber must include a statement in the product labeling stating the presence of natural rubber. FDA is requiring this statement because medical devices with natural rubber may pose a significant health risk to some consumers who are sensitized to natural latex proteins. The Branch expects to ensure that this requirement is being met as we review new labeling, especially for viscoelastic products that use latex rubber stoppers in their packaging.

Thank you.

DR. McCULLEY: Thank you.

We will now move on to the introduction of PMA 980031. Donna Lochner, Ashley Boulware -- oh, pronounced "Bouler"? It's not spelled that way.

(Laughter.)

DR. McCULLEY: Anyway, sorry, Ashley. I'll learn. Remember, I'm still in training.

Would you please introduce the PMA?

MS. LOCHNER: Yes, I'd like to just acknowledge the hard work of the review team on this PMA, in particular, Ashley Boulware, the team leader for the PMA, and I'd like to read into the record the review team who reviewed this document. First, Ashley Boulware was the team leader and the engineering reviewer; Dr. Malvina Eydelman, the clinical reviewer; Dr. Gene Pennello, the statistician; Susanna Jones, toxicology; Susan Gouge, microbiology; Jean Toth Allen, bioresearch monitoring; Carol Clayton, labeling; Ronald Swann, from the Office of Compliance, performed the good manufacturing practices review; and Mervin Parker from our PMA policy staff.

That concludes my comments. I will turn the floor over to Ashley Boulware.

MS. BOULWARE: Mr. Chairman, members of the panel, ladies and gentlemen, PMA P980031 has been submitted for the KeraVision Intacts Intrastromal Corneal Ring Segments. The Intacts consist of two half circles referred to as "ring segments." The Intacts are machined from Perspect CQ polymethylmethacrylate using techniques similar to those employed in intraocular lens manufacturing. The Intacts are available in three thicknesses -- 0.25 millimeter, 0.30 millimeter, and 0.35 millimeter. The product has a fixed outer diameter of 8.10 millimeter and a

width of 0.8 millimeter. Each segment has an arc length of 150 degrees and a cross-section that is hexagonally shaped.

A single positioning hole is drilled into the superior end of each segment to aid in the surgical manipulation. The Intacts are inserted between the layers of the corneal stroma through a small incision made in the periphery of the cornea. When surgically placed at approximately two-thirds depth into the corneal stroma, the Intacts reshape the corneal curvature by increasing the thickness of the cornea in the periphery. This peripheral thickening causes the interior curvature of the cornea to flatten, thereby correcting for myopia by lowering the optical power of the eye. The degree of corneal flattening achieved using the device is directly related to the thickness of the Intacts implanted.

The proposed indication is for the reduction or elimination of myopia of minus 1.00 diopter to minus 3.00 diopters at the spectacle plane in patients who are 21 years of age with documented stability of refraction as demonstrated by a change of less than or equal to 1.00 diopters for at least six months prior to the preoperative examination, and with preoperative myopia error ranging from minus 1.00 diopters to minus 3.50 diopters with 1.00 diopter or less of astigmatism.

The Intacts are implanted using a set of

surgical instruments designed by KeraVision specifically for this procedure. Hand-held surgical instruments are generally regulated as Class I devices exempt from 510k submission. FDA is currently considering the appropriate classifications for the KeraVision instruments.

The primary panel reviewers for P980031 are Drs. Grimmett, Sugar, and Van Meter. The sponsor has been advised of the questions and concerns raised by the primary panel reviewers and FDA's clinician, Dr. Malvina Eydelman. Following the sponsor's presentation, Dr. Eydelman will summarize issues from her clinical review.

Thank you, Mr. Chairman.

DR. McCULLEY: Thank you.

We'll move on to the sponsor presentation. A point, one, is that you have one hour for your presentation, and then just a point of clarification for me. I'd been advised that you had a movie of the surgical procedure that you were going to show and we were going to allow time for that. You're not going to show that? Okay.

I will now turn the floor to the sponsor.

MR. LOARIE: Good morning. I am Tom Loarie, chairman and chief executive officer of KeraVision. KeraVision was founded in 1986 to develop new solutions to correct common vision problems. We appreciate the opportunity to appear before you today with clinical

results for our first product, KeraVision Intacts for the correction of myopia.

KeraVision Intacts, shown here, are designed to reshape the interior surface of the cornea for the correction of myopia without compromising the central optical zone.

The outline for today's presentation is as follows. Darlene Crockett-Billig, KeraVision's vice president of regulatory affairs and clinical research, will present a regulatory overview. Dr. David Schanzlin, professor of ophthalmology, University of California at San Diego and the chief clinical investigator for KeraVision trials, will provide an overview of Intacts technology and an efficacy assessment. The safety assessment will be delivered by Dr. Michael Lemp, who is chairman of KeraVision's data and safety monitoring board. Dr. Lemp will also present an assessment of reversibility and adjustability before concluding today's presentation with a risk-benefit assessment of the Intacts product.

Now I would like to introduce Darlene Crockett-Billig.

MS. CROCKETT-BILLIG: Thank you, Tom.

I'd like to begin our regulatory overview with a description of the Intacts product. This non-laser, vision correction alternative reshapes the cornea

mechanically by adding material rather than by removing tissue from the cornea. Thickness of the device is a parameter which determines the refractive effect. Three thicknesses were evaluated in this PMA cohort. The proposed indication for this technology is for patients having -1.00 to -3.50 diopters of myopia with 1.00 diopter or less of astigmatism.

Intacts consist of two clear segments, each having an arc length of 150 degrees. They are manufactured from PMMA, which has a proven history as an ocular implant material. Intacts are placed in the corneal periphery outside the central optical zone. Because Intacts are an additive technology, they can be removed, if desired, which results in a reversal of the refractive effect. Through exchange procedures, they are also potentially adjustable.

I will now review the device's regulatory history. In April of 1991, IDE No. G910034 was approved for the initial product design. A 360 degree ring. Ten subjects were enrolled in this Phase I blind eye trial. This coincided with treatment of our first ten sighted eye subjects in Brazil. Our Phase II sighted eye trial with a 360 degree ring was approved in February of 1993. May of 1995 initiated the Phase IIa trial for our new 150 degree segment design with five thicknesses and a predicted range of -1.00 to -6.00 diopters.

As a result of these clinical data, a new nomogram was devised and the thicknesses were bifurcated into two separate trials. The 0.40 and 0.45 sizes were evaluated in an expanded Phase II trial using the revised nomogram. This trial was initiated in August of 1996.

The Phase IIIa trial for the 0.25, 0.30, and 0.35 millimeter Intacts was initiated in October of 1996 for -1.00 to -3.50 diopters.

In November of 1997, the Phase IIIb trial for the 0.40 and 0.45 Intacts was initiated along with a new 0.21 millimeter size. Data collection is currently ongoing for this trial. A modular PMA with twelve month data on the combined Phase II and Phase III cohort of 410 eyes for three thicknesses was submitted in July of 1998 and accepted for filing in August of 1998.

As I mentioned, the PMA cohort combines Phase IIa and Phase IIIa data for the 0.25, 0.30, and 0.35 thicknesses. Ninety eyes from Phase II were implanted and 359 eyes from Phase III, for a total of 449 eyes. The available post-operative follow-up ranges from 12 to 24 months.

Eleven clinical sites, listed here, participated in the Phase II and Phase III trials.

The Phase II and Phase III trials have been conducted with the oversight of a data and safety

monitoring board. Dr. Michael Lemp is the chairman of this board, and other members include Dr. Gary Foulks and Dr. Thomas Clinch.

The inclusion criteria for the PMA cohort was typical of most refractive surgery protocols, except that we required all subjects to have a best spectacle-corrected visual acuity of 20/20 or better. Likewise, the exclusion criteria was typical of most refractive surgery protocols, with consideration given to conditions affecting wound healing and overall corneal health.

A comprehensive list of ophthalmic tests were performed to evaluate the safety and effectiveness of the Intacts procedure. The tests included visual acuity, slit lamp, tonometry, refractions, and mesopic contrast sensitivity. Tests were conducted according to the schedule shown here. To help ensure standardization, extensive site training and certification were conducted prior to initiation of these trials.

The following tests were performed on subgroups for the PMA cohort. Spectral microscopy, central corneal sensation, A-scan, automated visual field, and slit lamp photography. All patients enrolled at a site were required to participate in the designated subgroup tests.

As we look at the demographics for the 449 evaluable implant eyes, we see that 51 percent were females

and 49 percent were males, the mean age was 39 years, the racial demographics are typical of contemporary refractive surgery studies in the United States.

Excellent accountability was maintained throughout the 12 month follow-up period. At the month 12 exam, 97.6 percent of subjects were evaluated.

The distribution of the PMA cohort is presented here. Of the 449 eyes who received Intacts, 410 eyes were evaluated at month 12. The remaining 39 subjects who were not evaluated at month 12 was for the following reasons -- 20 had the Intacts removed prior to month 12, 5 subjects were lost to follow-up, 5 subjects missed the month 12 exam, 4 subjects completed the month 12 exam but missed the analysis cutoff date, 4 subjects underwent an exchange procedure, and 1 subject had a single segment.

Subject enrollment was balanced by thickness within each of the 11 sites to achieve an overall balanced distribution.

DR. McCULLEY: While you're changing, let me point out to the panel that there is hard copy of her presentation in your folder, if anyone wants it and hasn't found it.

MS. CROCKETT-BILLIG: The initial Phase II nomogram, shown here, was based on Eye Bank eye research. Based on the preliminary data from Phase II, the nomogram

was revised for Phase III. The actual range of preoperative refractive error used for each sickness is specified here. As you can see, the actual range was from -0.75 to -3.875 for subjects in the PMA cohort.

I'd like to conclude by defining the study population evaluated in our PMA safety and efficacy analyses. Four hundred and fifty-four eyes were evaluated for safety. These data will be presented by Dr. Michael Lemp. For efficacy, I've already described the subject disposition which provides us with 410 evaluable eyes at month 12.

I would now like to introduce Dr. David Schanzlin, who is the director of keratorefractive surgery at the University of California in San Diego and chief clinical investigator for KeraVision's clinical trials. He will present an overview of Intacts technology and provide an efficacy assessment.

DR. SCHANZLIN: Thank you, Darlene.

Before I begin, I would like to state that I have served as a consultant to KeraVision for the last 12 years and I am the chief clinical investigator for the studies reported in this PMA cohort. My consulting fees are paid directly to the University. I recently acquired a small equity interest in the company, and KeraVision paid my way to this meeting. In my position on the full-time

faculty of the University of California at San Diego, I head up the refractive surgery service and I routinely perform various refractive procedures including PRK and LASIK.

Now let's review the basics of this new refractive technology for the correction of myopia. As shown here, the KeraVision Intacts are placed in the peripheral corneal stroma outside of the optical entrance pupil. The fact that the central optical zone is preserved is one of the primary advantages of the Intacts approach. Preservation of the central visual axis coupled with the fact that the Intacts can be removed allow for a refractive effect that is reversible and potentially adjustable.

The KeraVision Intacts consist of two clear micro thin PMMA segments, each having an arc length of 150 degrees. Each segment is precision lathe-cut to plus or minus 0.1 millimeter, and has a hexagonal cross-section that lies along a conic section. With a fixed outer diameter of 8.1 millimeters and an inner diameter of 6.8 millimeters, the Intacts have a large, clear central optical zone. Here, at the superior edge of each segment, you can see a small positioning hole which aids in surgical manipulation of the segments. As mentioned, three thicknesses, or sizes, are presented in this PMA for the correction of myopia.

Let's look at the role thickness plays in determining the device's refractive effect. Intacts act as passive spacing elements that change the arc length of the anterior corneal curvature. As shown here, placement of the Intacts in the periphery of the cornea causes local separation of the corneal lamellae. This results in shortening of the corneal arc length which has the net effect of flattening of the corneal curvature. When the Intacts thickness is increased, greater amounts of local separation occur, resulting in increased corneal flattening and greater refractive effect. Hence, the refractive effect achieved by the device is directly related to thickness.

To demonstrate how the Intacts create central corneal flattening, we have prepared this animation. Here you can see with the animation thickening of the ring segments. Watch the center of the cornea, how it flattens. Let's look at it again, however, and really this time, rather than looking at the center of the cornea, view the area in the mid-periphery and this time watch how the mid-periphery also flattens within the area inside of the ring itself. The importance of this observation relates to the maintenance of the cornea's natural prolate shape. Intacts are, to our knowledge, the first procedure for the correction of myopia that maintains normal corneal

asphericity.

The concept of arc shortening was verified by our early Eye Bank eye research. A nearly linear relationship between the device thickness and the change in corneal curvature was established, as demonstrated in this slide. This linear relationship has been confirmed and further refined by our clinical studies. With Intacts, each successive increase of 0.05 millimeters in thickness imparts an additional 0.70 diopters of corneal flattening.

Let's review quickly the surgical procedure for the Intacts procedure. First of all, a comment about the ease. This surgery is really very easy to master. Most surgeons are able to complete this surgery in between ten to fifteen minutes. In my hands, this is similar to the time that it takes me to do a LASIK procedure.

The procedure begins first by prepping and draping the eye in order to fully isolate the eyelashes from the surgical field. Next, using a geometric center as the reference, the corneal surface is inked with markings that indicate the incision placement site and the final positioning of the Intacts segments. Following pachymetry over the incision, a 15 degree diamond knife is set at two-thirds depth and a 1.8 millimeter peripheral incision is made along the incision mark. The vacuum centering guide is aligned on the central corneal mark and suction is

applied.

Next, we make the peripheral lamellar channels using a clockwise dissector. The dissector is a blunt instrument that is designed to preferentially dissect up rather than down if it ever gets out of corneal plane. A glide is inserted into a previously created lamellae pocket at the incision site, and the dissector is advanced under the glide to ensure that the lamellar dissection begins at the proper depth. The dissector is then rotated to create the peripheral lamellar channel.

DR. McCULLEY: Suction is maintained throughout that?

DR. SCHANZLIN: Suction is maintained throughout, and suction times run about one minute, one minute and fifteen seconds for both dissections.

DR. McCULLEY: Intraocular pressure during that time?

DR. SCHANZLIN: It's lower than LASIK. It's running around 80. The pupil occasionally will dilate and occasionally vision will blur.

The counter-clockwise dissection is then made in a similar fashion.

The Intacts segment is grasped with special forceps and inserted into the peripheral lamellar channel. There is no resistance encountered to this motion since the

channel has already been created. The segment is placed in its final position with a blunt Sinsky hook. It is positioned under the peripheral corneal markings, thus assuring its proper position not only in the outer extant, getting to the 8 millimeter outer diameter, but also keeping it free of the incision site.

The second segment is then inserted in a similar fashion. The wound is gently reapproximated with a single 11.0 nylon suture, the knot is buried, topical antibiotic and corticosteroid drops are instilled, and a clear shield is applied.

Let's now review the efficacy data from our PMA cohort of 410 subject eyes. To demonstrate the efficacy of KeraVision's Intacts for the correction of myopia, we assessed the variables summarized here -- uncorrected visual acuity, predictability based on cycloplegic refraction spherical equivalent, and stability of refractive effect. And, indeed, all efficacy endpoints were exceeded at month 12, both those specified in the two Intacts clinical protocols as well as those in the FDA guidance document for refractive surgery lasers which included predictability based on manifest refraction spherical equivalent. We recognize, however, that the laser guidance document was written for a range of -1.00 to -7.00 diopters and our data range was from -1.00 to -3.50

diopters. However, all of the data presented here today substantial exceed all of these endpoints.

Let's look at each of these endpoints in detail. The first protocol endpoint was uncorrected visual acuity. At one year, 97 percent of the patients had unaided visual acuity of 20/40 or better, 74 percent were 20/20 or better, and a remarkable 53 percent of the patients had unaided visual acuity of 20/16 or better.

The visual recovery at the Intacts procedure is quite rapid. On day 1, 57 percent of the patients were 20/25 or better uncorrected vision, 34 percent were 20/20 or better, and 13 percent were already 20/16. At month 1, at month 6, and month 12 we see continued improvement, and by month 12 over half of the subjects had achieved an impressive uncorrected vision of 20/16 or better. To our knowledge, no other refractive surgical procedure has such a high percentage of patients achieving better than 20/20 visual acuity.

Our next protocol endpoint was predictability of refractive effect based on cycloplegic refraction spherical equivalent. As shown here, 68 percent of the subjects were within half a diopter of intended correction, and 90 percent were within a diopter of intended correction. The protocol endpoints for predictability of refractive effect were exceeded by these Intacts

performance.

As I just noted, 90 percent of the subjects were within a diopter of the intended outcome at month 12. Of the 17 undercorrected subjects, only 1 was more than 2 diopters from intended. Similarly, only 1 of the 23 overcorrected subjects was more than 2 diopters from intended.

When we look at the deviation from plano, 92 percent of subjects were within a diopter of plano, only 1 of 23 undercorrected subjects had deviation from plano of more than 2 diopters, and, similarly, only 1 of 8 overcorrected subjects had a deviation from plano of more than 2 diopters.

As previously noted, the protocol endpoint for predictability based on cycloplegic refraction spherical equivalent was exceeded. Likewise, the Intacts predictability based on manifest refraction spherical equivalent is similar and also exceeded FDA guidance document for the refractive surgical lasers.

In any longitudinal analysis, it is important to look at a consistent population. Therefore, the same 408 subjects were analyzed at each exam point to document the percentage of eyes within plus or minus a half diopter and within plus or minus of 1.00 diopter of intended at 3, 6, and 12 months after surgery. We see that the

percentages achieved at month 3 remain constant over time.

The stability of manifest refraction over time was assessed using a constant population of the 384 subjects who had manifest refraction spherical equivalent results available at all exams from month 1 through month 12. We can clearly see that stability was achieved three months after surgery and was maintained through month 12.

Both the protocol and the FDA guidance endpoints for stability of refractive effect specify that 95 percent of subjects should have a change of less than or equal to 1.00 diopter of manifest refraction spherical equivalent between two refractions performed at least three months apart beginning at month 3. As we can see from this table, stability was reached at three months after surgery and confirmed at subsequent test intervals. So this endpoint was met for the cohort overall and for each of the three Intacts sizes at all time intervals.

Throughout the remainder of this presentation I will discuss the results within the recommended prescribing range for each of the Intacts thicknesses. To understand how the recommended prescribing range was derived, it is useful to examine the distribution of refractive errors for the cohort subjects by Intacts thicknesses.

As you can see, there was some overlap in the preoperative cycloplegic refractions between each of the

thicknesses. The preoperative range for the 0.25 millimeter size was -0.75 to -1.875 diopters. For the 0.30 millimeter size the range was -1.50 to -3.00 diopters. And it was -2.00 to -3.875 for the 0.35 millimeter Intacts.

To better assist ophthalmologists in selecting the appropriate Intact size for their individual patients, we have defined a recommended prescribing range, RPR, for each thickness. As indicated by the wide bracketing lines shown here, the ranges are contiguous but do not overlap. The ranges are based on the nominal predicted correction for each thickness plus or minus 0.35 diopters. For the 0.25 millimeter Intacts, the recommended prescribing range is a spherical equivalent of between -1.00 and -1.625. For the 0.30 millimeter, we have an RPR of -1.75 to -2.25. And for the 0.35 millimeter Intacts, the RPR is -2.375 to -3.00 diopters.

Of the 410 subjects in the overall PMA cohort, 317 were within this prescribed recommended prescribing range. The number of evaluable eyes within the recommended prescribing range for each thickness is also shown here and the distribution was approximately equal.

This table lists the uncorrected visual acuity performance by thickness within the RPR. We had 56 percent of subjects achieving excellent visual acuity at the level of 20/16 or better for all Intacts thicknesses. As we look

at the data by thickness, 63 percent of the 0.25 millimeter subjects, 54 percent of the 0.30 millimeter subjects, and 49 percent of the 0.35 millimeter subjects achieved this high level of uncorrected visual acuity. Both the protocol and FDA guidance endpoint called for 85 percent of the eyes achieving uncorrected visual acuity of 20/40 or better. Clearly, this criterion was easily surpassed by all three Intacts thicknesses.

More importantly, performance at the level of 20/20 or better was strong for each of the Intacts thicknesses, with 84 percent, 82 percent, and 66 percent achieving this level. And 78 percent of the RPR cohort overall achieved 20/20 or better visual acuity.

The Intacts demonstrated excellent predictability based on cycloplegic refraction spherical equivalent correction achieved at month 12. A tabulation of the predicted versus the achieved correction for the PMA cohort and for the RPR groups is shown here. As you can see, there's excellent correlation between these numbers for both the cohort and the RPR groups.

Predictability within the prescribing range was also good for each individual Intacts size. Both the protocol and FDA guidance endpoints specified that an outcome would be considered predictable if 75 percent of subjects were within a diopter of their intended

correction. This criterion was clearly exceeded for all three thicknesses.

Similarly, all three Intacts thicknesses surpassed the endpoint specified that 50 percent of patients should be within a half a diopter of intended correction. Having satisfied these endpoints for plus or minus 0.50 and plus or minus 1.00 diopter, we conclude that the Intacts procedure is, indeed, predictable.

In summary, we believe that the data from this PMA cohort have established the efficacy of the KeraVision Intacts for the correction of myopia with spherical equivalence from -1.00 to -3.00 diopters. We propose a recommended prescribing range for each Intacts thickness that is contiguous and non-overlapping. These ranges, shown here, are based on the nominal predicted correction plus or minus 0.35 diopters.

Thank you for your attention. I would now like to introduce Dr. Michael Lemp, president of University Ophthalmic Consultants of Washington and chairman of the data and safety monitoring board for the Intacts clinical trials.

Michael?

DR. LEMP: Good morning. Thank you, David.

Before I begin our assessment of safety, I would like to state that I have served as a consultant for

KeraVision for five years and that also I have no ownership interest in the company. I would also like to point out that as chairman of the DSMB board it is my opinion and that of the other members of the DSMB board that this clinical study was exceptionally well designed, conducted, and managed.

Now I'll turn to a consideration of the safety issues. To demonstrate the safety of the KeraVision Intacts for the correction of myopia, we assessed the safety variables which are summarized here. Indeed, all the safety endpoints were met at month 12, both those specified in the Intacts clinical profile as well as those in the FDA guidance document for refractive surgery lasers.

Now let's look at each of the endpoints in detail. The first criterion was best spectacle-corrected visual acuity. No subject had a best corrected visual acuity of 20/40 or worse at month 12, thus satisfying the endpoint. Best corrected acuity was maintained as 98 percent of the subjects were within nine letters of their preoperative value. Four subjects lost ten or more letters, and six gained ten or more letters at 12 months.

Again, the protocol endpoint for best corrected maintenance was satisfied for the cohort overall and for each of the individual Intacts thicknesses. There was no statistically significant difference among the Intacts

sizes.

This slide details the four subjects who had a loss of ten or more letters or two or more lines. It is important to note that each of these subjects was 20/20 or better at the last reported exam.

This slide compares best corrected acuity at month 12 to preop by level of visual acuity. All subjects had a best corrected acuity equal to or better than 20/32 at the month 12. The one subject who was 20/32 had lost only nine letters from the preop and so was not listed on the previous slide. By the next exam, this subject had returned to a preop baseline of 20/20.

But let's look here at the increase in the number of subjects having 20/10, 20/12.5, and 20/16 or better visual acuity. Of the subjects, 90 percent were 20/16 or better at month 12, and 99 percent w ere 20/20 or better. The improvement in best corrected acuity was statistically significant.

As I just noted, this improvement in best corrected acuity from preop was statistically significant. An analysis of the month 12 data compared to preop indicated that 19.5 percent of the subjects had an increase of five or more letters or one or more lines at best corrected acuity. Additionally, 34.6 percent had an uncorrected visual acuity equal to or better than their

preop best corrected visual acuity.

Now let's look at induced cylinder. Per the protocol endpoint, less than 5 percent of subjects were to have an induced cylinder greater than 2.00 diopters. No subject had a cylinder greater than 2.00 diopters. Here we see that 92 percent of subjects were within 0.75 diopter of their preoperative cylinder. This is considered to be within the range of measurement error for repeatability for manifest refractions per Zadnik, et al. Of those subjects, 15, who had a cylinder increase of greater than 1.00 diopter, 100 percent had a best corrected acuity of 20/20 or better, with 93 percent 20/16 or better. The uncorrected acuity for all patients was 20/32 or better, with 80 percent 20/25 or better. It is important to note that no subject had greater than 2.00 diopters of induced cylinder.

Mesopic contrast sensitivity both with and without glare was performed at all Phase III sites. A functional acuity contrast test chart was used with a view-in tester. The spatial frequencies tested were 1.5, 3, 6, 12, and 18 cpd.

The endpoint was met for all spatial frequencies tested both with and without glare. There was no mean decrease greater than 0.1 log unit. While some of the changes in spatial frequencies at the 1.5 and 6 cpd

without glare were statistically significant, they were not considered functionally significant. No clinically relevant changes were seen for any of the spatial frequencies evaluated.

Specular microscopy was a Phase III subgroup test with four sites participating. The Konan Robo non-contact specular microscopy unit was used. Three regions were assessed -- a central region, a 6 o'clock peripheral region, and a 10 o'clock peripheral region. Cell density, coefficient of variation, and percent hexagonality data were analyzed separately at a reading center at Emory University under the direction of Dr. Edelhauser.

In this photograph of an Intacts subject, we've illustrated three regions which we evaluated, they're in yellow, the central, 6, and 10 o'clock peripheral regions. It's important to note that the instrument used was designed primarily for central measurements. Measurements in the corneal periphery are normally difficult to obtain due to the angle of approach. The change in contour of the corneal surface and the peripheral area adjacent to the Intacts presented even more than the usual difficulties in obtaining the 10 o'clock images. These measurements were still taken, however, primarily to rule out changes in the cell morphology near the Intacts.

The protocol endpoint for endothelial cell

density specifies that the mean density should not decrease by more than 10 percent of the preoperative value. As this slide shows, all three regions clearly met the endpoint criteria, and all observed losses were substantially less than the specified maximum of 10 percent.

This slide compares endothelial cell density for the initial treated eyes and the untreated fellow eyes at month 6. Since untreated fellow eyes were eligible for surgery after month 6, this comparison was not available for later exam points. If we look at those eyes with a decrease greater than 10 percent, the central region shows that three of the initial or treated eyes and two of the fellow eyes had these readings. In the peripheral 6 o'clock region, seven of the treated eyes and six of the fellow eyes also had this. And in the peripheral 10 o'clock region, six treated eyes and five fellow eyes.

There were no statistically significant differences between the initial treated eye and the untreated fellow eye for any region evaluated. These data indicate that variability in the readings appears to be a reflection of the reproducibility of the measurement technique and not an indication of an ongoing safety issue.

The only data we were able to find in the literature on longitudinal peripheral endothelial cell densities assessed in a serial fashion was a paper by

Trocme, et al. in which peripheral cell densities were assessed preoperatively and following PRK. As you can see, the loss from preop to month 12 for the PRK was reported at 6.9 percent compared to 1.9 percent for the Intacts in the peripheral 10 o'clock position.

The coefficient of variation was actually improved at both month 6 and month 12 exams with the improvement at month 12 being statistically significant at the 0.02 level. The fact that the coefficient of variation was actually improved speaks against any morphological change associated with the Intacts procedure. No statistically significant change was seen in the percent hexagonality analysis. Also, there were no cellular morphologic changes that would indicate that the endothelium was compromised due to the Intacts procedure.

We now turn to the intraoperative clinical findings. The Intacts procedure was successfully completed 98.9 percent of the time. The intraoperative adverse events rate was 0.2 percent. One subject experienced an anterior chamber perforation. This was related to either an incorrect diamond knife setting and/or a deviation in the pocketing technique that resulted in an overly deep pocket. The event was not related to the product, and the subject has fully recovered.

There were six subjects who experienced

intraoperative ocular complications as defined in the protocols. three of these six complications were related to a deviation in the surgical protocol, two were related to subject movement, and the remaining intraoperative complication was related to an allergic reaction to the antiseptic material used. None of these intraoperative complications was related to the device.

There were five safety related adverse events during the twelve month reporting period. Two anterior chamber perforations, one which was just discussed as an intraoperative event during the initial implant procedure, and a second one which occurred during an exchange procedure. Both incidents were related to deviations from the surgical procedure; that is, incorrect knife settings and pocketing technique. One subject had an infection during the early post-operative course which completely resolved. One subject had a decrease of two or more lines of best corrected acuity over two consecutive exams which subsequently resolved. And one subject had a shallow placement of the temporal segment which was subsequently removed. The nasal segment remains in place and the subject has had a good visual outcome.

Looking at a breakdown of the adverse events by protocol, we see that three of these adverse events occurred in Phase II, for an adverse event rate of 3.3

percent. The two adverse events in Phase III resulted in an adverse event rate of 0.6 percent, and a combined adverse event rate for the PMA cohort is 1.1 percent.

This slide provides the visual outcomes for the five adverse event subjects. The case of infection was resolved and the subject is stable with 20/16 best corrected vision. As a result of this early Phase IIa adverse event, an infection prophylaxis guideline was implemented in March of 1997. No infections occurred in the Phase IIIa subsequent to the guidelines' implementation. As previously noted, the subject with a shallow placement of the temporal segment still has the nasal segment in place. Her uncorrected acuity is 20/20, and best corrected acuity is 20/12.5. The subject with a loss of two or more lines of best corrected acuity for two consecutive exams was stable at month 12 interim exam with no loss of best corrected acuity. The subject with an anterior chamber perforation after the initial surgery has a best corrected acuity of 20/12.5 and is scheduled for a second surgery. The subject with an anterior chamber perforation during the exchange procedure subsequently had the Intacts removed. The subject recently underwent a successful exchange procedure and the best corrected acuity is now 20/20.

It is important to note that the best corrected

acuity for all of these adverse events patients was 20/20 or better at their most subsequent and most recent exam. No additional adverse events have occurred for the contralateral eyes in the PMA cohort. And the total enrollment now stands at 735 eyes, and the combined adverse event rate is 0.7 percent.

Central corneal sensation was a subgroup test involving nine sites. A Cochet-Bonnet anesthesiometer was used. A subject was considered to have a significant loss if the decrease in central corneal sensation was 20 millimeters or more from the preoperative exam. To our knowledge, there are no studies available which validate the reproducibility of this methodology.

With that in mind, let's review the data. At month 12, 5.5 percent of the subjects had equal to or greater than 20 millimeters reduction in central corneal sensation. It's interesting to note that six of the thirteen subjects here were from one site, perhaps indicating some subjective variability in the method. It is also important to mention that no subject had a complete loss of corneal sensation, or had an epithelial defect, or had any clinical sign of neurotrophic keratitis. At their most recent exam, all of the 13 subjects have returned to their preoperative baseline.

We evaluated the reduction in central corneal

sensation by thickness and found no statistically significant relationship.

The incidents of clinically significant complications noted between month 9 and month 12 was low. We saw the following. Four subjects with a loss of equal to or greater than ten letters or two lines of best corrected acuity; three have returned to within ten letters or two lines, the remaining subject was 20/20 with an eleven letter loss. The one subject who had a best corrected acuity worse than 20/25 has subsequently returned to baseline. Fifteen subjects had an induced cylinder greater than 1 diopter. The range was between 1.25 and 1.50 diopters for twelve of the fifteen, and 1.75 diopters for three of the fifteen.

As noted earlier, all of these subjects had a best corrected acuity of 20/20 or better with 93 percent 20/16 or better. All cylinder subjects had an uncorrected acuity of 20/32 or better with 80 percent 20/25 or better. No subject had more than 2 diopters of induced cylinder.

As we look at neovascularization, I'd like to note that all of the cases were in the region of the incision site. What we saw between the month 9 and month 12 interval were six subjects with pannus, four of whom had had preexisting pannus. Five subjects had a single deep vessel. None of these vessels were progressive. All five

subjects had a history of contact lenswear, and one subject had a deep vessel preoperatively, two had preexisting pannus, and one of the five had the vessel resolved by the month 12 exam. One subject was reported to have a persistent epithelial defect located temporally which was attributed to dry eye during the month 12 test interval. This was not considered to be related to the device. The onset was at month 9 and the incident had been resolved by month 12. One subject had an onset of Uveitis at the month 9 interim exam, it had completely resolved by the month 12 exam. Thirteen of the 237 subjects experienced a reduction in central corneal sensation of equal to or greater than 20 millimeters at the month 12, and all 13 have returned to within 20 millimeters of their preoperative central corneal sensation reading.

Twenty-three, or 7 percent of subjects, have reported having "always" and "severe" visual symptoms at month 12. These symptoms included difficulty with night vision, blurry vision, double vision, glare, halos, and fluctuating distance vision. Although exact comparisons are difficult to obtain due to differences in reporting methodologies, these numbers are similar to those reported for other approved refractive technologies.

We evaluated the data by thickness for the 23 subjects who reported visual symptoms, and you can see the

data here. It's important to note that 11 of the 13 subjects with 0.35 millimeter Intacts had a 1 diopter or more deviation from plano. As you recall from Dr. Schanzlin's presentation, many, 29 percent, of our enrolled 0.35 subjects were outside the proposed recommended prescribing range for this thickness.

The question then becomes what is the significance of these visual symptoms. We looked at the following data to answer this question. How many of the 23 subjects with "always" and "severe" symptoms at month 12 elected to have their second eye treated? Eleven, or 48 percent, had a contralateral eye procedure. We also saw that three of the twenty-three subjects went on to request a removal procedure, and four had exchange procedures.

We analyzed the data to determine probable reasons for visual symptoms. Post-operative deviation from plano had a statistically significant relationship with frequency and severity of difficulty with night vision, diplopia, and blurry vision. A statistically significant relationship was seen between the month 12 manifest refractive cylinder and the frequency and severity of halos, diplopia, fluctuating vision, and blurry vision. Other variables associated with visual symptoms included mesopic pupil diameters of 7 millimeters or greater, and preoperative RGP contact lens wear most likely associated

with some degree of corneal warpage.

Finally, the results of a self-administered patient survey indicated that 90 percent of the subjects were satisfied with their initial Intacts procedure, and 95 percent of those who had had bilateral procedures.

Let's move on to a consideration of reversibility and adjustability. As previously mentioned, one of the unique features of this additive technology is that it can be removed, if desired. And because there's no surgical invasion of the central visual axis of the cornea, a reversal of refractive effect is possible. Intacts can be easily removed in a brief outpatient procedure. It takes approximately about five minutes. No clinically significant complications or sequelae have been associated with the removal procedure. And this feature provides a unique option for restoring a patient's eye to its previous optical performance.

The proposed claim of reversibility is based primarily on two criteria, preservation of a subject's best corrected visual acuity and the ability of the subject to return to within 1.00 diopter of the preoperative refraction. These criteria were derived from the FDA guidance document.

Of the 34 removal procedures, one, and infection case, was removed for safety reasons, fourteen

were removed due to dissatisfaction with the correction achieved, sixteen for dissatisfaction due to visual symptoms, and three for other removals. One subject in this latter category had the Intacts removed from two eyes due to FAA restrictions for pilots having "experimental" procedures. And this subject had an uncorrected acuity of 20/16 in one eye and 20/25 in the other. One subject was explanted due to an anterior chamber perforation during the exchange procedure and has subsequently undergone a successful exchange procedure.

Of the 34 removals, comparison to the preoperative status is provided for 28 subjects with three months of postremoval data available. Per the protocol, patients were exited after month 3, hence our selection of this time period for postremoval analysis. All subjects were within ten letters or two lines or better of their preoperative best corrected acuity, and all subjects were 20/20 or better.

Postremoval predictability data indicates that 81 percent of the subject eyes returned to within a half a diopter of their preoperative manifest spherical equivalent, and 96 percent returned to within 1.00 diopter. The one subject with a manifest spherical equivalent greater than 1.00 diopter compared to preop actually had an improvement in the manifest spherical equivalent.

Here we see the 26 subjects, or 96 percent, that returned to within 1.00 diopter of their preop manifest spherical equivalent. The one subject who was not within the 1.00 diopter actually had a decrease in his refractive error.

In looking at the manifest refraction cylinder at month 3 postremoval exam, we see that 100 percent of the subject eyes returned to within 1.00 diopter, and 93 percent returned to within a half a diopter based on manifest refraction cylinder by the month 3 postremoval exam.

This slide shows the stability of the manifest refraction within 1.00 diopter over time. All subjects were stable within 1.00 diopter manifest spherical equivalent by the month 3 postremoval.

The uncorrected acuity reversibility data indicate that 93 percent of subject eyes returned to within two lines or better of their preoperative uncorrected vision, and 82 percent returned to within one line or better of their preoperative uncorrected acuity.

Reversibility of visual symptoms is defined as returning to the same or better level of severity and frequency as compared to the preoperative level of the referenced symptoms. By symptom, 81 to 96 percent of subjects had a reversal in their visual symptoms upon

removal. To assess reversibility, we looked at several refractive criteria.

Accounting for subjects who were within or improved from preop, 89 percent were within a half a diopter of manifest spherical equivalent, a half a diopter of cylinder, and one line of best corrected acuity; 100 percent were within three-quarters of a diopter of manifest refraction, three-quarters of a diopter of cylinder, and one line of best corrected acuity. Obviously, 100 percent were well within the criteria derived from the FDA guidance document listed here.

In review, 100 percent of subjects maintain a best corrected acuity of 20/20 or better, all were within 1.00 diopter or better of their preoperative manifest spherical equivalent, 100 percent had a stable postremoval refraction from month 1 to month 3, and 93 percent were within a half a diopter of their preoperative manifest refraction cylinder, and a majority of visual symptoms were reported at levels equivalent or better than their preoperative levels.

Adjustability of the Intacts refractive effect is achieved through an exchange procedure in which the Intacts of one thickness are removed and substituted for new ones of a different thickness. Twelve, or 2.7 percent, of the subject eyes had an exchange procedure as of the

November 12, 1998 clinical update. All 12 exchanges were for undercorrection. The subjects were eligible for an exchange procedure after six months and provided they met the specified protocol criteria.

This slide provides a comparison of pre-exchange and post-exchange deviation from plano. Post-exchange, over half of the subjects shifted to within 1.00 diopter of plano. We saw fewer subjects with a deviation greater than plano after their exchange procedure, and no subject greater than 2.00 diopters post-exchange. Also, 73 percent of the subjects were 20/40 or better, and 55 percent were 20/25 or better after their exchange procedure.

All subjects had increased refractive effect following an exchange procedure, 73 percent had an improved uncorrected acuity, and three exchange subjects went on to have their Intacts removed due to continuing undercorrection.

In conclusion, let's consider the overall risks and benefits of the procedure. The performance data for Intacts were excellent, allowing us to conclude that the Intacts effectively reduce myopia between 1.00 and 3.50 diopters for subjects with 1.00 diopter or less of astigmatism. The uncorrected visual outcomes were outstanding, and best corrected visual acuity was

maintained. It is important to note that no clinically significant harm to any subject occurred. The rapid visual recovery was demonstrated and that effect appears to be reversible upon removal.

Reviewing the procedure itself, we see that it does not compromise the central optical zone, that the cornea's natural physiological shape is maintained; i.e., an aspheric or prolate surface. Since Intacts correct myopia by mechanical rather than surgical remodeling of the cornea, no tissue removal is required and no long-term corticosteroid therapy is required. And finally, the procedure is relatively easy to learn and yields consistent refractive results.

As with any procedure, there are some risks. Patients may need another procedure if the results are not satisfactory. Visual symptoms may occur following the procedure, visual symptoms primarily related to the post-operative deviation from plano and cylinder. Patients may experience induced astigmatism which typically decreases over time, however, the visual acuity does not seem to be significantly affected. Infection is a risk with any surgical procedure. It is important to note that the adverse event rate however was quite low.

All safety endpoints have been met. It has been demonstrated that Intacts are well-tolerated in the

cornea. And no patient has had a clinically significant loss of best corrected acuity.

All the efficacy endpoints have been met or exceeded. Excellent visual acuities have been achieved. The performance is predictable. And the refractive effect is stable.

The proposed indication for use of the KeraVision Intacts is for the reduction or elimination of myopia of -1.00 to -3.00 diopters at the spectacle plane in patients who are 21 years of age or older, with a documented stability of refraction as demonstrated by a change of less than or equal to 1.00 diopter for at least six months prior to the preoperative exam, and with preoperative myopic error ranging from -1.00 to -3.50 diopters with 1.00 diopter or less of astigmatism.

And so in summary, the KeraVision Intacts we believe represents a safe and effective alternative for the correction of myopic errors. The benefit-risk ratio is very favorable with excellent visual outcomes, the ability to return a patient's eye to its preoperative optical performance, and a very low adverse event rate. The clinically relevant point for any refractive surgery procedure is how well do patients see. And these patients see extremely well. Over half of the subjects have corrected visual acuities of 20/16 or better. As chairman

of the Data and Safety Monitoring Board, I believe this study has demonstrated the safety and effectiveness of the Intacts for the indicated use.

This concludes our presentation. Thank you for your attention.

DR. McCULLEY: Thank you.

We will recess and take a 15-minute break. Please note the clock. It is 9:37.

(Recess.)

DR. McCULLEY: We're now going to begin with the clinical review by Dr. Malvina Eydelman. But prior to that, Ms. Thornton has a couple of introductions.

MS. THORNTON: Before we proceed, I would like to introduce to you and to our panel and our staff here the two people that we've waited for and that came in for the properdin of the sponsor's presentation. They have had a great deal of difficulty getting here and we really appreciate their perseverance.

The first person I would like to introduce to you is Dr. Renee Middleton. She is our interim consumer representative who has graciously agreed to attend in the place of our panel consumer representative, Ms. Lynn Morris. Dr. Middleton comes to us from the Ear, Nose, and Throat Devices Advisory Panel. She is an assistant professor in the Department of Counselling and Counselling

Psychology, and director of Human Resources and Outreach in the College of Education at Auburn University in Auburn, Alabama. Thank you very much for your perseverance. We really appreciate your coming here and taking up our consumer representative banner for today.

The other person I'd like to introduce to you is a voting member of our panel, Dr. Jose Pulido, professor and chair of the Department of Ophthalmology at the University of Illinois Eye and Ear Infirmary in Chicago, Illinois. Welcome to you also, Dr. Pulido.

Thank you, Dr. McCulley.

DR. McCULLEY: Malvina?

DR. EYDELMAN: Good morning. I would to thank the sponsor for providing me with a copy of their presentation prior to this meeting, allowing me to avoid redundancy in my presentation. Today I will, therefore, only highlight some points for panel consideration and will not present a comprehensive review of the clinical study in this PMA.

The sponsor has eloquently summarized their specular microscopy outcomes in the presentation you just heard. I would like to bring to your attention some additional outcomes. For all implants, the mean central cell loss at 12 months was 0.41 percent. Since contact lens users are known to experience a transient rise in

endothelial cell density after discontinuation of contact lens wear that might offset the initial decrease in endothelial cell density, the sponsor was asked to stratify the cell density outcomes by preoperative use of contact lenses. The mean central endothelial cell loss over one year for contact lens wearers was 0.15 percent, and 0.98 percent for those who wore glasses preoperatively.

No operative eye in this study had a decrease in cell density of 10 percent or more in the central region. Stratifying the central loss by implant thickness revealed no statistically significant differences.

Peripheral cell density outcomes, however, differed significantly from central. For all implants, the mean loss was 1.8 percent at 6 o'clock, and 1.9 percent at 10 o'clock position. Thirteen eyes had a decrease in peripheral cell density of 10 percent or more. Six subjects had a decrease at the 6 o'clock position, and seven at ten. Out of the thirteen eyes with a decrease in the peripheral endothelial cell density of 10 percent or more, four had 0.25 millimeter implant, three had 0.30, and six had 0.35 millimeter implant.

Cell density analysis stratified by thickness revealed statistically significant differences between the thicknesses for change between preop and month 6 as well as preop and month 12 for 10 o'clock region only. At 10

o'clock location, between preop and month 6, 12 percent of eyes implanted with 0.35 millimeter Intacts had cell density loss of greater than 10 percent as compared to 2 percent for 0.25 and 3 percent for 0.30 Intacts. At the same location, between preop and month 12, 15 percent of eyes implanted with 0.35 ring had cell density loss of greater than 10 percent as compared to 2 percent for 0.25 Intacts, and 3 percent for 0.30.

Furthermore, the mean peripheral cell change at twelve months for the 10 o'clock position also showed statistically significant differences between the thicknesses. There was 4.95 percent loss associated with 0.35 millimeter implant as compared to 0.24 percent increase with 0.30, and a 1.5 percent loss associated with 0.25 ring.

Given that the device in question is a corneal implant, the sponsor was requested to perform several analyses to try to establish lack of progression of endothelial cell loss. The mean endothelial cell density at the preoperative month 6 and month 12 exams was compared for each of the corneal regions. There was a statistically significant decrease in endothelial cell density between month 6 and month 12 for all three regions. Sponsor compared findings at the central region to the expected decrease in normal eyes reported by Bourne, et al., of 0.6

percent per year and found the differences from month 6 to month 12 not to be statistically significant.

Peripherally, at 6 and 10 o'clock, mean change from month 6 to month 12 was 1.4 percent and 1.1 percent respectively. The expected rate of decrease in the peripheral corneal region of normal subject eyes could not be found in the literature, so a comparison of the mean peripheral change to the rate of loss in normal eyes was not possible.

The panel is being asked to consider the outcomes of all the endothelial cell density analyses and comment on whether sufficient assurance of safety is currently available or whether additional analysis and/or additional longitudinal follow up is needed prior to conclusion.

Visual symptoms in the study were assessed for frequency of occurrence as well as magnitude. Analysis of visual symptoms reported as "often" or "always" between the preoperative and month 12 exams for all thicknesses combined reveals some interesting findings. Glare frequency increased from 1.7 to 9.7 percent, halos from 0.3 percent to 11.9 percent, difficulty with night vision from 5.9 percent to 17.3 percent, blurry vision from 1.5 to 12.2 percent, sensitivity to light increased to 7 percent from 3.4, double images from none preoperatively to 6.7 percent

at month 12. All of the visual symptom increases was statistically significant with the exception of fluctuating distance vision.

There was statistically significant changes between the frequency of double images, fluctuating near vision, and fluctuating distance vision between preoperative and month 12 exams among different thicknesses.

Double images were reported as occurring at a frequency of "often" or "always" at the month 12 exam by 3.7 percent of subjects with 0.25 Intacts, 5.5 percent with 0.30 Intacts, and 10.9 percent with 0.35 Intacts. Fluctuating near vision was reported as occurring at a frequency of "often" or "always" by 1.8, 1.8, and 7.3 percent for the 0.25, 0.30, and 0.35 millimeter Intacts respectively. Fluctuating distance vision was reported as "often" or "always" by 0.9, 1.8, and 7.3 percent of subjects with the three rings, as seen on this slide.

Magnitude of visual symptoms in this study, combining moderate and severe symptoms, is presented here. Glare occurred at 16.1 percent, halos at 17.2 percent, difficulty with night vision 19.1 percent, and blurry vision at 15.9 percent. Results for light sensitivity, double images, and fluctuating vision of moderate or severe magnitude are seen here.

Among Intacts thicknesses, a statistically significant difference in symptom magnitude was seen as well. Double images were reported at a magnitude of moderate or severe at month 12 by 6.1, 6.9, and 15.3 percent of subjects with the 0.25, 0.30, and 0.35 millimeter Intacts respectively. Fluctuating distance vision was reported at a magnitude of moderate or severe by 4.7, 8.8, and 14.3 percent of subjects with the three different sizes.

The panel is being asked to consider visual symptoms data in their recommendations for safety outcomes of each of the three thicknesses of the Intacts. Aspects of this data the panel feels are important to be present in the labelling need to be identified.

Reductions in central corneal sensation that were 20 millimeters or more from the preoperative baseline was seen for 9 percent of subject eyes at month 6, 5 percent at month 12, 3 percent at month 18, and 2 percent of the eyes at month 24. Of the subject eyes with reduction of central corneal sensation that were 20 millimeters or more, 13 out of 24 subject eyes examined at month 6, and 6 out of 13 subject eyes examined at month 12 were observed at a single clinical site.

Review of the implant videotapes for these subject eyes suggest that the reduction in central corneal

sensation may have been related to the surgical technique. It appears that in each of these cases there may have been some excessive manipulation of the incision site during the pocketing procedure which may have contributed to the loss of central corneal sensation. The panel's recommendation for appropriate labelling addressing corneal sensation loss is requested.

The sponsor has already presented the predictability data for the overall device as well as for each of the thicknesses. This slide is meant just to draw your attention to the fact that the predictability of the 0.35 millimeter implant to achieve both plus or minus half a diopter and plus or minus 1.00 diopter of intended is statistically lower than the thinner implants.

The average achieved corrections for each implant thickness in the PMA cohort were as follows: 0.25 millimeter, 1.48 plus or minus 0.52 diopters; for 0.30 millimeter, 2.07 plus/minus 0.56; and for 0.35 millimeter, 2.76 plus/minus 0.69 diopters. As you have already heard, the sponsor has revised the recommended prescribing range for each implant size. While the sponsor's nominally predicted corrections of 2.00 and 2.70 diopters closely mimic the mean achieved correction for both the 0.30 and 0.35 millimeter implants, for the 0.25 millimeter Intacts the sponsor is recommending a nominally predicted

correction of 1.30 diopters even though the mean achieved correction was 1.50 diopters. Panel members are being asked to consider this in their recommendations for labelling.

The combined recommended prescribing range for all three thicknesses currently spans from -1.00 diopter to -3.00 diopters of myopia. The proposed indication for use for this device reads as follows: "KeraVision Intacts are intended for the reduction or elimination of myopia of -1.00 to -3.00 diopters at the spectacle plane in patients who are 21 years of age or older, with documented stability of refraction as demonstrated by change of less than or equal to 1.00 diopter for at least six months prior to preoperative examination, and with preoperative myopic error ranging from -1.00 to -3.50 diopters with 1.00 or less of astigmatism."

There were 40 eyes treated with 0.35 millimeter Intacts that had preoperative CRSE greater than 3.00 diopters. Outcomes for these eyes are presented on this slide. As you can see, while only 43.6 percent of these attained CRSE within half a diopter of preop, 87.5 percent achieved 20/40 or better uncorrected visual acuity. Please consider these outcomes in your recommendations regarding the appropriate upper myopic range for the indication for use statement.

As you have already heard, out of 34 eyes in the removal cohort of this PMA there has been one safety related removal due to infectious keratitis, 16 removals occurred due to dissatisfaction with visual symptoms achieved. Visual symptoms that prompted removal were night vision, glare, halos, and double images, a finding that's consistent with the outcomes of subjective assessment of visual symptoms. Fourteen removals occurred due to dissatisfaction with the correction, seven of these occurred due to dissatisfaction with correction secondary to induced astigmatism. Among the three removals classified as "Other," one was associated with a deferred exchange procedure secondary to anterior chamber corneal perforation with a diamond knife during an attempted exchange procedure.

The mean duration of ICRS implant time prior to removal was 10.3 months. The removals due to dissatisfaction related to visual symptoms tended to occur at an earlier time point than removals due to dissatisfaction with outcomes related to correction. Even though refractive stability for this device was established to occur by six months, most removals occurred after month 6. This was one of the factors that prompted FDA to request a minimum of 12 months follow-up prior to PMA submission.

This submission provides distribution of Intacts removal by thickness. Five removals occurred in eyes with 0.25 millimeter Intacts, 10 in 0.30, and 19 removals in eyes with 0.35 millimeter Intacts. Thus, 56 percent of removals occurred in the 0.35 millimeter Intacts eyes. This is consistent with the earlier discussions of greater visual symptoms and decreased accuracy of correction achieved with the 0.35 millimeter device.

Sponsor's reversibility claim is based upon data from 28 eyes that have completed a month 3 postremoval exam. Six of these exams were not conducted within the designated exam window and ranged in time from two to nine months postremoval. Thus, three months postremoval data within the designated exam window is available for 22 eyes. No data analysis beyond three months postremoval is currently available.

Twenty-seven out of 28 eyes analyzed by the sponsor had manifest refractive cylinder data. All of these returned to within plus or minus 1.00 diopter manifest refraction cylinder by the month 3 postremoval exam. For the one eye with no MR cylinder value available at month 3 there was an increase in cycloplegic refractive cylinder of 1.25 diopters. Analysis of the seven subjects who had an increase of greater than 1.00 diopter of manifest cylinder with the implant shows that upon removal

the change in the resultant cylinder as compared to preop varied from minus 0.25 diopters to plus 0.75 diopters.

Removal subjects from Phase IIa reported in the severity of visual symptoms. At the preoperative exam, the severity of all key symptoms were rated as none or mild. At the month 3 postremoval exam, two subjects reported a total of three key symptoms as severe. All remaining key symptoms were reported as none or mild. Out of the 22 eyes with three months postremoval data, 19 had both month 1 and month 3 exams. All of these 19 eyes were within plus or minus 1.00 diopter of MRSE, and 12 of these eyes were within plus or minus of half a diopter MRSE.

Panel members are being asked for their assessment of the reversibility data. Specifically, is MRSE plus or minus 1.00 diopter in 19 eyes between one and three months postremoval exams sufficient to establish stability at three months postremoval? Is the data currently available for the removal cohort sufficient to make the reversibility claim for this device? If not, how much data and what length of follow-up is needed before such a claim can be established?

There have been a total of 12 exchange procedures as of 11-12-98. As you have already heard, all subjects to date were exchanged for reasons related to undercorrection. It is important to point out that 11 of

the 12 exchanges performed involved switching to 0.40 and 0.45 millimeter Intacts, thicknesses which are not currently available and are not subject for evaluation in this PMA.

In the analysis of the post exchange outcomes, sponsor has combined data from all the most recent post exchange exams. These ranged from seven days to eighteen months post exchange. The outcomes of this most recent post exchange data analysis shows a range of the change in MRSE achieved as a result of exchange to span from 0.12 diopters to 1.50 diopters. Unfortunately, the sponsor has not yet been able to identify a precise nomogram for predicting the ideal size of the Intacts needed for exchange. As a result, residual post exchange MRSE in the 12 eyes range from minus 2.00 diopters to plus 0.25 diopters. Three subjects had their Intacts subsequently removed due to continuing undercorrection.

The panel is being asked to consider data from these exchange procedures in consideration of sponsor's claim for adjustability of refractive effect.

Current proposed labelling for this device reads as follows: "An analysis was performed to assess the percentage of subjects who achieved enhanced visual performance at month 12. The results indicate that 21.5 percent of patients had a post-operative UCVA better than

the preoperative BSCVA, 32.7 percent of patients achieved their post-operative UCVA better than 20/20 and equal to or better than the preoperative BSCVA, 19.5 percent of patients achieved their post-operative BSCVA that was better than the preoperative BSCVA. These results indicate that the KeraVision Intacts may be capable of increasing the resulting power of the cornea to provide for enhanced visual capabilities for some patients. Patients with the KeraVision Intacts may be able to achieve better visual acuity than they could achieve with their prior methods of vision correction. This finding may occur because the natural prolate shape of the cornea has been maintained inside the central optical zone for these patients."

There were 80 eyes with a month 12 BSCVA that had better than their preoperative BSCVA. Phase II data is analyzed in terms of lines change, and Phase III in terms of letter change. For the 18 eyes in this category in Phase II, the mean BSCVA line change was 1.1 plus or minus 0.3, and the mean BSCVA letter change for 62 eyes in Phase III subjects was 6.2 plus or minus 1.7 letters.

This enhanced visual performance statement is based upon a change of less than two lines of Snellan VA. In another analysis in this PMA, in calculating the amount of BSCVA loss following the procedure, the sponsor did not count the one line loss as clinically meaningful. The

sponsor believes that this inconsistency can be explained by skewed preoperative distribution and the fact that the ETDRS chart only measures to a visual acuity of 20/10, thus limits accordingly a gain of 10 or more letters for those subjects with preoperative BSCVA better than 20/16.

This slide contains a summary of the month 12 UCVA compared to the preoperative BSCVA for the other two categories of the enhanced visual performance claim. The mean line change is 1.1 and the mean letter change is 3.5 for subjects with post-op UCVA better than preop BSCVA. The mean changes for the last group are 0.3 lines and 2.7 letters.

In light of this discussion, panel members are being asked to comment on the enhanced visual performance section in the labelling.

This concludes my comments and I will now restate the questions for panel consideration.

Question 1. "Do the outcomes of the endothelial cell density analysis presented in this PMA provide reasonable assurance of safety for all three thicknesses of the Intacts? What, if any, additional data are needed to make this decision?"

Question 2. "Do the assessments of visual symptoms provide reasonable assurance of safety for all three thicknesses of the ICRS?"

Question 3. "Do the reports of corneal sensation losses provide reasonable assurance of safety for all three thicknesses? What, if any, additional data are needed to make this decision?"

Question 4. "The range for the average correction achieved with 0.25, 0.30, and 0.35 millimeter Intacts is from minus 1.48 diopters to minus 2.76 diopters. Does the achieved correction data support requested indication for patient population with preoperative myopic error ranging from minus 1.00 to minus 3.50 diopters with 1.00 or less of astigmatism?"

Question 5. "Do the safety and effectiveness outcomes support approval of 0.25, 0.30, and 0.35 millimeter Intacts? Is distinct labeling warranted for any one of the three proposed thicknesses?"

Question 6. "Is the current data in the removal cohort sufficient to support reversibility claim? If not, what is the minimum number of eyes and the minimum length of follow-up that you recommend for this assessment?"

Question 7. "Is the current data on exchange procedures sufficient to support the claim for adjustability of refractive effect? If not, what is the minimum number of eyes and the minimum length of follow-up that you recommend for this assessment?"

Question 8. "The sponsor would like to make a claim of 'enhanced visual performance' in their labeling. Do you feel that the data in this PMA support this claim?"

Thank you very much. This concludes my presentation.

DR. McCULLEY: Thank you.

Do any of the three primary reviewers have visual aids? Okay, then can we turn the lights back up again.

If we could go to the primary reviewers, we're going to take them in the order that they appear on the agenda. For those of you who don't have an agenda in front of you, that will be Dr. Sugar, then Dr. Van Meter, then Dr. Grimmett.

Dr. Sugar?

DR. SUGAR: Thank you.

The sponsors are to be complimented for their organized and complete presentation and their responses to the FDA requests, and, likewise, Dr. Eydelman is to be complimented for her complete and very insightful review. I have to apologize for the redundancies in this process, so I'm going to review some information that has already been reviewed.

Four hundred and fifty-two patients were enrolled in the initial portion of the study, first eye

portion, 449 of which underwent implant procedures. Ultimately, many second eyes were operated upon, leaving a total of 735 eyes undergoing implants. Most of the data was reviewed, however, for just the first 449 eyes. Demographics were consistent with other refractive studies, and the accountability was very high with 410 of 420, or 97.6 percent, available for study at twelve months. The other 29 not eligible included 20 who had the implants removed, 4 exchanged, 1 who had a single segment removed, and 4 who had analyses out of window.

The efficacy exceeded guidelines for all measures, although as Dr. Schanzlin mentioned, it should be kept in mind that the guidelines are for correction of myopia up to minus 7.00 diopters and this study attempted to correct only up to 3.00 diopters of myopia. At month 12, for the 0.25 millimeter segments 83.7 percent had 20/20 or better acuity, and 99.3 percent 20/40 or better uncorrected visual acuity; for the 0.30 millimeter segments this was 77.5 percent and 97.1 percent; and for the 0.35 millimeter segments 60.6 percent and 93.4 percent. And with the ultimate recommended prescribing ranges, the figures are even a little bit higher.

An attempted versus achieved scattergram was never presented and data on specific patients with greater than 3.00 diopters of myopia preoperatively were not

presented to me for analysis. This would be useful. Predictability, however, as defined by plus or minus 1.00 diopter of manifest refractive spherical equivalent, was 92 percent at twelve months and 69 percent plus or minus 0.5 diopters and this decreased with increasing segment thicknesses.

Stability appeared to be achieved between three and six months, and this was acceptable.

The sponsors make an efficacy claim for enhanced visual performance, which Malvina just reviewed, or hyperacuity. The three definitions Malvina went through. They conclude that "these results indicate that the keraVision Intacts may be capable of increasing the resolving power of the cornea to provide for enhanced visual capabilities for some patients. Patients may be able to achieve better visual acuity than they could achieve with their prior methods of vision correction." However, it should be noted that 13.9 percent lost one or more lines of BSCVA while 19.5 percent gained one or more at twelve months. Admittedly the ability to gain lines is limited since many patients were 20/12.5 or 20/10 preoperatively. The percentage of contralateral, unoperated eyes that also gained best corrected visual acuity was not presented.

Given that examiners and subjects were not

masked as to treatment and there was no specific wording that I'm aware of for testing so that examiners and subjects would likely to have been more eager to have good outcomes in the treated eye, this phenomenon may not be real. The fact that a number of examiners apparently commented on how well patients saw may reflect a difference between this procedure and other refractive procedures rather than truly enhanced performance since the visual axis was not incised or ablated.

In terms of safety, this data has been reviewed and safety appears to not be an issue in terms of contrast sensitivity or loss of best spectacle-corrected visual acuity.

Induced cylinder likewise decreased as time went on, although the increased likelihood of induced cylinder with increased ring thicknesses should be mentioned in the package inserts.

Endothelial cell density and morphology were assessed in a subgroup. Cell density overall decreased by a mean of less than 1.5 percent which was not statistically significantly different rom the 0.6 percent cell loss per year found by Bourne in normal patients. But 13 of 110 patients however did show a greater than 10 percent cell loss at one year. While the mean cell loss is not clinically significant, patients with a 10 percent cell

loss are of concern and follow up endothelial analyses on these patients may be worthwhile. It is conceivable that especially with the thicker implants that there is continuing flection of the cornea and flection of the posterior surface of the cornea that may induce continuing endothelial cell loss. Perhaps a post-PMA analysis of these patients and of future patients would be worthwhile.

Changes in pachymetry were not significant. Channel deposits and lamellar channel haze and peripheral vascularization do not appear to be significant. There was central clouding noted at 1 and 2-plus level in two patients and this rapidly resolved and appears not to be significant.

The corneal sensation data is difficult to be certain about. There were 25 of 259 patients, or 9.3 percent, who lost 20 millimeters or more of sensitivity at six months while 13 of 237, or 5.5 percent, showed 20 millimeters or more loss at twelve months. Interestingly, seven of these thirteen did not show the loss at six months but did show it at twelve months, which is certainly hard to explain. The changes however do not appear to be practically important.

Visual fields were unchanged. Intraocular pressures were not an issue.

Subjective symptoms are an issue. The severity

of symptoms was assessed in Phase II subjects while severity and frequency were assessed in Phase III. At twelve months in Phase III important changes were noted in difficulty with night vision, blurry vision, halos, double image, and glare. Double vision and fluctuating vision increased with ring thicknesses and frequency of them increased with ring thicknesses. This information must be reflected in the physician and patient labeling.

And 90 percent of patients were somewhat or strongly satisfied with outcomes at twelve months. Levels were higher, 95 percent for patients undergoing bilateral implants, but this increased percentage presumably reflects the fact that patients who are satisfied with their first eye are more likely to go on and have surgery on their second eye.

Adverse events included one infection with staph epidermidis which resolved with removal of the segments. It is uncertain whether removal of the segments was necessary or not. All patients with adverse events recovered 20/20 or better best spectacle-corrected visual acuity in the study.

Reversibility of effect, 36 of 449 patients, or 8 percent, underwent implant removals; 12.2 percent in Phase II, and 7 percent in Phase III. Twenty-one removals were because of symptoms of glare, fluctuating or blurred

vision, halos, or poor night vision; seven were due to under or overcorrection; five due to induced astigmatism, one due to infection; one due to perforation, and one because of this mentioned patient who had his removed because the FAA did not accept them.

No patient lost best spectacle-corrected visual acuity or was worse than 20/20, and all patients with available data were plus or minus 1.00 diopter of their preoperative refraction, and 82 percent were plus or minus a half diopter. Two patients however had severe trouble with night vision, double images, or fluctuating vision. All others had either no or mild symptoms. So the procedure does appear to be reversible.

In terms of lens exchanges, in my review I found that 12 eyes underwent exchanges, all for undercorrection. Three of these were later removed because of persistent undercorrection. All exchanges but one were with segments of 0.40 millimeters or 0.45 millimeters, sizes which were not part of this PMA.

Improvement in manifest refractive spherical equivalent was noted in all patients but the magnitude varied from only 0.12 diopters with a 0.35 to a 0.45 exchange to 1.50 diopters with a 0.35 to 0.40 exchange. Patient numbers, data on the larger ring sizes, and predictability of outcomes are insufficient to allow

approval of wording suggesting that undercorrection can be improved through ICRS exchanges.

With these findings mentioned, I recommend approval with conditions, and we will discuss this more later. This ends my review.

DR. McCULLEY: Thank you.

Dr. Van Meter? Feel free to be as detailed or as summarizing as you feel comfortable with.

DR. VAN METER: This is Woodford Van Meter. Mr. Chairman, do you want us to go through the answers of the questions proposed now or will we do that later?

DR. McCULLEY: No, we'll do that later. But if you have something incorporated in your review that addresses it, then do that. But we're not going to go through those specific questions now.

DR. VAN METER: Woodford Van Meter. I also would like to thank the sponsors for a thoroughly organized presentation, and thank Dr. Eydelman for a very detailed clinical review that made this reviewer's job much easier than it otherwise might have been.

The accountability of this study I thought was very reasonable with 452 patients initially enrolled, 449 eyes comprising the patient cohort, as previously mentioned. Thirty-nine eyes did not have a month 12 examination, leaving 410 eyes which completed the month 12

exam as the basis for the data presented. Of the 39 eyes missing the month 12 exam, there were 20 removals, 4 exchanges, 1 single segment removal, and only 5 patients out of this cohort lost to follow-up. The data were presented for 97.6 percent of the 410 implanted eyes. This is very reasonable accountability.

In the effectiveness category, there were three efficacy endpoints reviewed, which were uncorrected acuity, predictability, and stability. At twelve months, uncorrected visual acuity showed 74 percent of subjects 20/20 or better, and as might be expected, the findings were slightly better with the lower thickness implants than the higher thickness implants. The patient numbers were comparable between the three sizes. Overall, 15.2 percent of patients saw 20/40 or better preoperatively, but only 13.8 percent were in the lower myopia group that received the 0.25 millimeter rings.

I think it is significant that FDA guidance calls for 85 percent uncorrected visual acuity of 20/40 or better, but we're comparing apples and oranges because the guidance document was really issued for lasers which correct up to 7.00 diopters and in this particular device correction only up to 3.50 diopters is reasonable. However, the data did show a significant improvement in uncorrected visual acuity compared to preop in all three

groups.

The predictability analyzed for manifest and cycloplegic spherical equivalent again showed better predictability at twelve months with a 0.25 millimeter height than the other two. The revised prescribing indications when stratified by ring height showed that the manifest refraction plus or minus 1.00 diopter was achieved in 95.5 percent with a 0.25 height, 85 percent with a 0.35 height. Again, this reaches FDA guidance document parameters with the proviso already mentioned.

I would like to make a comment however that the reversibility of this implant device probably makes additional risk acceptable and these devices do appear to be reversible.

As might be expected, the predictability is slightly better in the lower myopia range. And as was mentioned in the revised document that we received in late December, the fact that the greater scleral elasticity in younger patients probably accounts for the improved effect in younger patients rather than older patients as was initially suspected.

Certain subjects appeared to achieve an enhanced level of vision following the implants -- 21 percent achieved a post-operative uncorrected acuity that was better than preoperative best spectacle-corrected

acuity, 19.5 percent of patients achieved a post-operative best corrected acuity better than preop. There was approximately 60 percent overlap between patients in these two groups.

I believe that labeling is reasonable to describe the enhanced visual capabilities observed in some patients, but the lack of predictability for which patients are likely to see better and the obvious problems from fitting these patients that are undercorrected with any contact lens to correct residual refractive error, which might be your best option if they don't want to wear glasses, make labeling a very critical issue that I think we should discuss. I think it's fair for the company to represent the improved effect, but I don't think any claims can be made regarding this effect.

The sponsor states stability by manifest refraction was obtained by month 3 because 97 percent of eyes had MRSE at month 6 plus or minus 1.00 diopter of the month 3 examination. I don't think stability is a major concern. In the inclusion criteria patients had to have a manifest refraction plus or minus a diopter within six months prior to surgery. Therefore, stability after the procedure is no worse than stability before the procedure.

Safety issues are discussed in terms of best spectacle-corrected acuity, induced cylinder, contrast

sensitivity, and endothelial cell counts. With best spectacle-corrected acuity, there was very minimal risk of losing best spectacle-corrected acuity. At month 12, three patients had a BSCVA worse than 20/20. All patients had BSCVA 20/20 or better at 18 and 24 months. The number of subjects that lost BSCVA was comparable to the number of patients that gained BSCVA, suggesting a normal statistical distribution in effect. At six months, seven subjects lost two or more lines of BSCVA, none had BSCVA worse than 20/32, and nine had improved BSCVA. At twelve months, four patients had worse BSCVA but none worse than 20/25, and six actually had improved BSCVA.

For induced cylinder, the percentage of patients that had an induced cylinder greater than 1.00 diopter at twelve months was 3 percent with a 0.25 implant, 7.3 percent with a 0.30, and 11.7 percent with a 0.35. Again a slant that would not be unexpected. Since no subject had greater than 2.00 diopters of cylinder and since the procedure is potentially reversible, I believe this complication can probably be accepted as a learning phenomenon of implantation surgery. And it should be covered in labeling that the possibility of induced cylinder with the higher ring thicknesses, i.e., 0.35 millimeters, probably is worth including in the preoperative consent.

Endothelial specular cell counts. The slightly increased endothelial cell loss at twelve months in the 0.35 millimeter group is of some concern. The percentage of patients with greater than 10 percent loss at month 12 was 2 percent with a 0.25 implant, 3 percent with a 0.30, and 15 percent with a 0.35 implant. However, given the limitations of endothelial cell counts, the variations in cell counts in even normal individuals, and the lack of concrete data on what peripheral cell loss means in normal subjects -- which to my mind makes me wonder why we collect peripheral cell loss because we're not certain what we want to do with this data -- in addition to the known fluctuations in cell counts in contact lens wearers, the seriousness of the problem, or whether it is a problem at all, is not known.

I believe that additional follow up should be collected on the 0.35 millimeter subjects to gather more data to determine what the potential problem might be down the road. But I note that even at the 10 o'clock cell count, which is where most of the problem seems to have appeared, is taken through the edge of the implant and it is reasonable to suspect that there is some distortion in the measurement here. So I think postmarket follow-up for the 0.35 implants with endothelial cell counts is probably reasonable.

Contrast sensitivity testing showed minimal adverse effect of the implants on glare and low contrast acuity. I thought it was acceptable.

There were five adverse events reported in the four hundred and fifty-four patients. One patient with infectious keratitis, one patient had shallow placement of the stints, two patients with anterior chamber perforations -- I will not repeat these because they've been discussed.

The corneal sensation loss probably means that labeling should include some notation that partial loss of corneal sensation that may be temporary is possible. The clinical significance however of this loss of corneal sensitivity is not known.

Twenty-nine of the 31 removals in the cohort were due to patient dissatisfaction with the device. There have been 34 removals in 725 subject eyes implanted through May of 1998 for a 4.7 percent removal rate. The sponsor has presented sufficient data on reversibility, with an 87 percent return to manifest refraction of plus or minus a half a diopter, to make reversibility a reasonable claim.

That concludes my presentation except for the proposed questions and I will hold that until later.

DR. McCULLEY: Dr. Grimmett, you have a very scholarly and outstanding review. If you could stress areas where in more detail where you bring up new points

and where you're in agreement, if you could state that you're in agreement, if it needs fine tuning, then state the fine tuning.

DR. GRIMMETT: Yes, I refer everyone to my detailed comments of 13 December. I will not belabor the point, and to avoid redundancy I will just state some highlights of issues that I felt important. But I will refer everyone to the 13 December comments that I made. I will try to summarize my comments into four main issues -- regarding the data in general, safety issues, efficacy issues, and regarding labeling for the thicker implants.

Regarding the data in general, I echo the comments of Drs. Sugar and Van Meter regarding complimenting the sponsor for an extraordinarily comprehensive data presentation. I appreciated it. I have concerns that the follow-up percentage in month 18 and 24 are low overall and have the potential for sample bias. So my comments will be restricted to month 12 data. I don't believe that the data from those longer intervals may represent the entire cohort for sample bias reasons.

Regarding safety issues, I will comment on five highlights. First, regarding distance best spectacle-corrected visual acuity loss without glare. It is important to note by way of background that a loss of 2 or more Snellan lines, that is ten letters, has been

recognized as being clinically meaningful because a gain or loss of one line can occur from one exam to another in unoperated eyes, particularly in individuals who can see 20/10, 20/12, or 20/16. Using this definition of greater than two lines of loss as clinically meaningful, the patients in this study had an acceptably low rate of loss; that is, 4 out of 410, or 1 percent, loss greater than two lines at 12 months.

The second safety issue regarding the corneal endothelium, my major concern concerns the 0.35 millimeter implant. There was a statistically higher rate of mean cell loss, that is, approximately 5 percent, at the 10 o'clock position. I calculated instantaneous annual cell loss rates and it is a footnote in the longer document, footnote 9, and determined that at a 5 percent cell loss rate, if we started with a cell count of 2,700 cells per square millimeter, if that were continuous annually, in order to reach 800 cells, which is the threshold for which we may start seeing clinically significant corneal edema, it would take approximately 23 and three-quarters years to reach that. That would be concerning for younger patients because that may occur during their lifetime. Hence, due to that reason, I believe that longer term follow-up is warranted for the 0.35 millimeter implant peripherally. Perhaps this is best achieved by postmarket surveillance.

The third issue on safety is regarding corneal sensation. It has been previously discussed that 13 out of 237, or 5 percent, had decreases greater than 20 millimeters in central corneal sensation. But, very importantly, no patient with a central corneal sensation loss had corneal staining of any kind. Dr. Lemp in his slides indicated that all 13 of these patients returned to normal, which is quite reassuring. However, I would state that in my opinion appropriate labeling should include a statement regarding the potential for altered corneal sensation in select patients, if it's not already done.

Regarding the subjective assessment by subjects, it has been pointed out that the frequency of all visual symptoms increased at month 12 to a maximum of 17 percent for difficulty with night vision. And regarding the magnitude of visual symptoms, up to approximately one in five patients complained of moderate or severe visual symptoms at month 12. These findings suggest that optical quality has been altered in select patients.

I agree that labeling should reflect tables that show the frequency data with "often" and "always" in the categories and in the magnitude data "moderate" and "severe." Simply reporting the "always" and "severe" in my mind downplays important visual symptoms that occur in a fair number of subjects within this study. Assuming that

labeling reflects these data, I think that the visual symptoms are acceptable.

Regarding the reversibility of this data, I appreciated the updated data from the manufacturer that increased the follow-up percentage to 82.4 percent, 28 out of 34 eyes, at three months following removal. That's up from 62 percent follow-up in the original submission that I reviewed. This essentially removes the specter of sample bias. I believe that greater than 80 percent follow-up is reasonable.

I believe that appropriate labeling regarding reversibility should reflect the fact that the data is limited to three months. We're only talking about 28 out of 34 eyes that had the procedure removed. The long-term stability of the refraction is not known. I have concerns that three months is not long enough to fully establish the stability of the refraction postremoval. And, number three, unless data is available to the contrary, the suitability of these eyes for further refractive procedures is unknown. I did not locate data that indicates that they're suitable for further work.

The third point regarding efficacy issues, first regarding uncorrected visual acuity. Uncorrected visual acuity has been previously shown to be an important predictor of patient satisfaction, and, indeed, 97 percent

of these patients had 20/40 or better uncorrected visual acuity at month 12. I thought that was excellent.

Regarding the stability of the manifest refraction spherical equivalent, the majority of the patients achieved, that is greater than 80 percent achieved plus or minus a half diopter from visit to visit. The procedure does appear to be stable.

I believe that the labeling should specifically state the percentage of patients changing plus or minus a half diopter from visit to visit sense the level of preoperative myopia is low. Hitting the mark 95 percent of the time plus or minus 1.00 sounds very impressive until we consider the fact that some of these patients went into this procedure with myopia as low as minus three-quarters of a diopter. A two diopter spread for those patients I don't believe is acceptable. As long as the labeling reflects what is plus or minus a half, I think that would be sufficient.

Regarding the predictability, for the thinner implants, 0.25 and 0.30, the procedure is capable of achieving plus or minus a half of intended in approximately three-quarters of patients at 12 months. Similar to my comments on the stability, I believe the labeling should indicate predictability within a half diopter of intended. And I had a comment regarding that the mean achieved

correction should equal the nominally predicted correction but I believe one of Dr. Schanzlin's slides altered the prescribing range for the 0.25 millimeter implant. The data reflect a mean achieved correction of approximately 1.5. In the original submission, the nominally predicted correction was 1.3. I believe that should be reconciled, but it may have already been done.

Regarding the hyperacuity phenomenon, I believe in order to be consistent throughout the report, or any report, that the definition of a clinically significant gain or loss of Snellan vision should remain the same within the report. I don't think it's fair to report loss greater than two lines and report gains greater than one letter, because in doing so you're minimizing the downside and emphasizing the upside. I would go with the generally accepted clinical definition of a two line cutoff. Moreover, Dr. Sugar's point regarding the potential for bias in the post-operative vision measurements is valid and may, indeed, skew the data toward better post-operative vision measurements. Hence, I endorse only reporting changes in the measured visual acuity greater or equal to two lines.

The sponsor has an argument that the data may be skewed because it is difficult and/or impossible to measure patients with a two line gain for those patients

starting with 20/10 or 20/12.5. That is a valid point. However, I think the issue is moot. The number of eyes by my review that started in that circumstance is only approximately 20 eyes total. That's only 5 percent of the eyes in the total study started with that circumstance. So I don't believe that issue matters.

Regarding adjustability, I believe the number of exchanges is too low for claims of adjustability. Additionally, I believe the implant sizes utilized for many of the exchanges are outside the range of those reported in this study. Therefore, the data do not support claims of adjustability.

My final issue is with regard to the labeling of the 0.35 millimeter implant. I believe that the thicker implant will require different labeling. As detailed in my 16-page document of 13 December, there are eight issues that I believe should be specific to the 0.35 millimeter implant.

One, the endothelium, the 0.35 millimeter implant, as previously mentioned, had a 5 percent mean loss over 12 months. That was a statistically significant difference from the others. I believe that should be mentioned.

Two, regarding induced cylinder greater than 1.00 diopter, there is an increasing trend with higher ring

thicknesses and that was a statistically significant difference.

Three, regarding explants, there is a trend for a higher rate of explantation due to refractive or optical aberrations with the thicker implant. That is 19 of 34 eyes with 0.35 millimeter were explanted.

Four, with regard to the frequency of visual symptoms, the thicker implant has an increasing trend for double images and fluctuating distance and near vision. That difference was statistically significant.

Five, regarding the magnitude of visual symptoms, the thicker implant has increasing trend for double images and fluctuating distance vision. That also was statistically significant.

Six, regarding uncorrected visual acuity, the thicker implant has lower success rates for achieving 20/20 or 20/40 uncorrected vision. That was statistically significant.

Seven, regarding the stability of the manifest refraction spherical equivalent, the thicker implant has lower proportion of subjects plus or minus a half diopter from visit to visit. That finding was statistically significant.

Eight, finally, regarding predictability, the thicker implant has a lower predictability for both plus or

minus a half of intended and plus or minus one diopter of intended. That also was statistically significant.

I'll conclude my comments there and wait for the questions. Thank you for your attention.

DR. McCULLEY: Thank you. That was excellent. I thank all three of the reviewers for excellent and thoughtful reviews. It made the job much easier for all the rest of us.

At this point, what we'd like to do is recall the sponsor to the table, and the purpose of this portion of the proceedings is for panel to ask sponsor specific questions relative to the PMA and for sponsor to respond directly to the questions posed. It is not an opportunity for the sponsor to introduce additional issues, unless they're brought up by panel.

So if the sponsor would please return to the table. Is sponsor ready?

MS. CROCKETT-BILLIG: Almost.

DR. McCULLEY: Let me know when you're ready. You have your water bottle. Are you ready?

MS. CROCKETT-BILLIG: Sponsor's now ready.

DR. McCULLEY: We'll open the floor now for panel to query the sponsor.

Dr. Van Meter?

DR. VAN METER: I'd like to ask two questions.

One, it has to do with the surgical procedure. When you are doing an exchange, is it necessary to use the instrument that separates the corneal stromal lamella in the same way that you do a primary procedure or can you pull one implant out and just place larger ones in place without having to recarve the channel?

MS. CROCKETT-BILLIG: This is Darlene Crockett-Billig from KeraVision. It is not necessary to redissect the channel. The segments are simply removed and new segments of a different size are reinserted into the existing channel.

DR. VAN METER: Okay. Well, then the one perforation that occurred on an exchange procedure, did that involve the device actually being driven through Descemet's membrane into the anterior chamber?

MS. CROCKETT-BILLIG: No. That adverse event was related to an incorrect diamond knife setting. When the initial incision was reopened, it was related to a diamond knife setting.

DR. VAN METER: So the perforation occurred on the initial incision reopening.

MS. CROCKETT-BILLIG: Yes, that's correct.

DR. VAN METER: Then my second question is there was one perforation that I presume was understood to actually dissecting the lamella, the one perforation that

occurred in the primary procedure. Was that a diamond knife problem or a dissection problem?

MS. CROCKETT-BILLIG: I'll have our director of clinical, Dan Beck, respond to that question.

MR. BECK: This is Dan Beck, director of clinical for KeraVision. In reference to your question of one of the two operative posterior corneal perfs, yes, upon review of the videotape in that particular case, we observed that there was additional dissecting of the incision that really deviated from the protocol, and we attribute the dissection ultimately to that underlying cause.

DR. VAN METER: So the incision was too deep?

MR. BECK: It may have been too deep. It may have been incised too deep. That was not obtainable from the video.

DR. VAN METER: I guess I'm trying to conceptually understand how the perforation occurred, and that was when you actually put in the device that creates the channel.

MR. BECK: Now, it did not -- it's hard to tell from the video when exactly the perforation did occur. It may have been ultimately due to a too deep diamond knife setting or too excessive manipulation of the incision prior to insertion.

DR. VAN METER: Because one of the concerns I think a surgeon would have is that the effect of this is clearly dependent on how deep the device is inserted, and it probably makes a difference that approximately two-thirds thickness is a nice approximation, but whether you want 200 microns or 300 microns or 400 microns between the device and Bowman's probably makes a difference in the effect. I presume this is something that you all have looked at.

MS. CROCKETT-BILLIG: I'd like to call Dr. David Schanzlin to the podium to address that.

DR. SCHANZLIN: We have looked at thickness based on --

DR. McCULLEY: Identify yourself.

DR. SCHANZLIN: I'm sorry. Dave Schanzlin, representing KeraVision.

We have looked over the last several years at all of our results, looking at the effect of depth of the implant versus effect, and there doesn't seem to be an effect as far as efficacy. There is a concern, of course, that you be deeper than 50 percent in these cases, and so that is a concern for the surgeon who's doing the surgery.

The incident discussed here, where the surgeon set the diamond knife at two revolutions -- in other words, he was off by more than 300 microns -- is something that

certainly should be addressed in training surgeons how to do that.

Then the other question you had was on the exchange procedure. If an exchange is done early, within I would say the first six to nine months, a Sinsky hook can easily open the incision, and you can find the channel and then grab it with the positioning hole with the Sinsky blunt section up, and draw out the ring with ease. If it is longer than that, you sometimes will have to reincise the incision if it's scarred, and that's what happened in this case where a diamond knife was used.

DR. VAN METER: Okay.

DR. McCULLEY: So your perforations were with your incisions, not with the insertion of the segments.

DR. SCHANZLIN: True. The other case that was presented here, the question was was it the incision or was it the initial pocketing with the Saurez spreader? Was it a deep incision to begin with and then the Saurez then caused the dissection? It's hard to tell from the video which of those two steps, but it was not from the device itself.

DR. VAN METER: Thank you.

DR. McCULLEY: Dr. Wang?

DR. WANG: Ming Wang. I've been formulating this question all morning after hearing the presentation

and all the reviewers' comments. Under this question, I have three subquestions under it. The question is does the 0.35 millimeter group present as a distinct, correlatively different group compared with the other two?

My question is supported by three comments. Number one, there appears to be grossly doubling of visual symptoms and frequencies in the .35 group compared with the other two. For example, diplopia in the .3 group is 6.9 percent and the .35 group is 15.3 percent and endothelial loss is higher. So therefore, there appears to be a grossly doubling of problems with the .35 group.

The second subquestion, everybody mentioned about possibly the necessity of squeeze, so to speak, of the guidelines of the guidance document for a lower range of correction. The reference has been for the 1 to 7 diopter correction, and the issuing question is 1 to 3 diopter. My question is does a squeeze in the guideline in the guidance document for this lower range result in a questioning of this .35 group quality?

For example, the guidance document asks for 75 percent within 1 diopter, though grossly overall, all three groups included, you have 91 percent, which is far above the 75 percent within the 1 diopter, but the .35 group, 83 percent, which is higher than 75 percent, but not that high. Then 50 percent within .5 diopter final

predictability, though all three groups combined is 71 percent, which is much higher than the 50 percent, but the .35 group again is 62 percent, which is marginally higher.

So the question again is if we need to squeeze the guidance document for the low range, would that result in the questioning of this .35 group?

Third, and the last subquestion in the .35 group, is is there any data -- I understand it's ongoing -- about the .4 and .45 groups? I understand it's not included in the present review. Is there any data or indication that would suggest there might be problems with the thicker group, and because it resulted in more stress, therefore, since it is a continuum from .35 to .4 to .45, which would again result in a questioning of this .35 group, because it is the closest to the .4 and .45 groups.

Therefore, in summary, the question is does the .35 group present as a distinct, correlatively different group compared with the other two?

DR. McCULLEY: Sponsor?

MS. CROCKETT-BILLIG: I'm just taking notes on the question. All right. To make sure I understood what you said --

DR. McCULLEY: Can you speak more into the mike, please?

And everyone, please, each time you speak,

please identify yourself.

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. To repeat the question as I understand it, you asked basically does the 0.35 group present a distinct and correlative difference as compared to the other two thicknesses that we evaluated?

Then underneath that you had three subcategories. The first category that you discussed was having to do with the performance based on visual symptoms. The second category had to do with basically the performance of the .35 as compared to the other two thicknesses. The third, you requested information on the ongoing trials with the .40 and .45 thicknesses to see if that was suggesting a safety problem.

One moment. We're bringing up the data.

As you recall from Dr. Schanzlin's presentation, 29 percent of the subjects in the 0.35 group were undercorrected. They were outside of the RPR range. Here's a slide that was presented by Dr. Lemp providing the visual symptoms at month 12. Now, as we go to look at by ring thickness --

DR. McCULLEY: Dr. Rosenthal?

DR. ROSENTHAL: I frankly think that the issue was well discussed by both the sponsor and the FDA and the primary reviewers, and I'm not sure we're going to get much

more out of reviewing their data.

DR. McCULLEY: I think one issue that was --

DR. ROSENTHAL: This is more a comment about a philosophical issue relating to the larger segment, and I appreciate the comments made, but I'm not sure a response is going to elucidate any greater clarity for the panel.

DR. McCULLEY: I think that there are some philosophical points that have been brought up by the reviewers that I agree I'm not sure that we'll resolve. There was one point that was brought up that I think might be of use, certainly, and that is do you have any insights from the .40 and .45 that might help us assess the .35, and whether there are trends that then continue in the negative direction past the .35 that would cause concern?

DR. ROSENTHAL: May I? This is Dr. Rosenthal. I think the PMA does not really address the two greater segments and --

DR. McCULLEY: But Ralph, I think the PMA does mention the .40 and the .45. Sponsor brought it up. I think that information from that could be of value to the panel in assessing the safety and effectiveness of the .35.

DR. PULIDO: I agree.

DR. McCULLEY: They may not have data. If they don't have data, fine, but I think it's reasonable for us to ask if they have information that can help us in our

deliberations. If they don't have the data, they don't have it, but I think it's perfectly appropriate for us to ask this, since they introduced it into the discussions and it is reality.

DR. ROSENTHAL: This is Dr. Rosenthal. I appreciate your need to want to know, but it's really not part of the PMA and a formal presentation is not being given to you. They can give you a general statement, but I think it would be inappropriate to start bringing formalized evaluation to us when no one has had a chance to even look at it, including our own reviewer.

Certainly, I would think if you want to make a general statement about it, please do.

DR. McCULLEY: Could I clarify the point then that it would be inappropriate for sponsor to bring or present data, but if there are general comments that can be made, that we would appreciate those general comments.

MS. CROCKETT-BILLIG: All right. Darlene Crockett-Billig. On the data that we have available in our ongoing Phase IIb and Phase IIIb trials with the 0.4 and 0.45 millimeter thicknesses, the endpoints are met, as specified in our protocol for the .40 and .45 thicknesses. When we look at within the recommended prescribing range, we have 98 percent of patients 20/40 or better and 67 percent 20/20 or better.

DR. McCULLEY: I guess the points that Dr. Wang brought up were more targeted toward symptoms, endothelial loss, and the like.

MS. CROCKETT-BILLIG: We're collecting that data. We don't have that available at this point in time on the thicker ring sizes.

DR. McCULLEY: Fair enough.

Dr. Macsai?

DR. MACSAI: This is Dr. Macsai. I have a series of questions for the sponsor if the chair will allow.

The sponsor has talked about the comparison of post-op vision with preop best spectacle-corrected vision, and I am aware that Dr. Eydelman brought up in her review the question of preop contact lens vision. Does the sponsor have comparison of post-op uncorrected visual acuity with preop contact lens visual acuity, either soft or rigid?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. Your question is does the sponsor have available uncorrected visual acuity data comparing outcomes with preop contact lens wearers versus post-op contact lens wearers?

DR. MACSAI: Yes, that is my question. In other words, did you measure best contact lens-corrected

visual acuity preop?

MS. CROCKETT-BILLIG: No, we did not.

DR. MACSAI: So then you don't have that comparison?

MS. CROCKETT-BILLIG: The protocol specified for best spectacle-corrected visual acuity.

DR. MACSAI: My next question is in regard to the incidence or rate of fluctuating distance vision, double images, and halos. With halos, if you look at the often and always percent of patients with these symptoms post-operatively, there is 11.8 percent patients with post-op complaint of halos, compared to .3 percent preop, a 37 times increase. Yet if you look at the same symptom under mesopic conditions with pupil size less than 7 millimeters or greater than 7 millimeters, there appears to be no statistically significant difference in the patients' perception of halos. Therefore, I ask you if these halos are directly due to this device.

The same thing can be seen for double images, where the percent noted by patients is 6.7 percent often/always post-operatively, zero percent preoperatively, and approximately equal under mesopic conditions, and for fluctuating distance vision the increase is from 1.1 percent preop to 3.3 percent post-op, or three times, where it is approximately equal with the pupil being 7

millimeters, greater or less than 7 millimeters. So is it the device that's causing these visual symptoms?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. We did our analysis on visual symptoms --

DR. MACSAI: Well, I saw your data when you presented it, but it doesn't answer the question.

MS. CROCKETT-BILLIG: We found that the statistical significance was primarily related to post-operative deviation from plano.

DR. MACSAI: So it's the post-operative deviation from plano that's causing the halos, double images, and fluctuating vision? Because these things don't seem to change dependent upon pupil size, which you would expect them to.

MS. CROCKETT-BILLIG: I'd like Dr. Michael Lemp to address that question, please.

DR. LEMP: Thank you. Michael Lemp, representing KeraVision.

Dr. Macsai, in response to your question, what we found was the thing that was statistically associated with these symptoms was deviation from plano and induced cylinder, and you correctly point out that in some of these symptoms there did not appear to be a statistical association between pupil size and this.

If you have residual cylinder, you would expect

to have some of these symptoms irrespective of pupil size, and so the induced cylinder was statistically associated with these symptoms, in addition to deviation from plano, so that the pupil size probably may play a role under certain conditions, but the farther away you get from the refractive effects, you may have these symptoms induced without the influence of the pupil size.

DR. MACSAI: So Dr. Lemp, are these symptoms due to induced cylinder or uncorrected cylinder?

DR. LEMP: Well, we think that the statistical association that the analysis of the data showed was an association between undercorrection and induced cylinder, so both of those show an association.

DR. MACSAI: Dr. Lemp, could the induced cylinder be corrected with spectacles? Because it seems that contact lens fitting when this device is in your cornea might be a challenge.

DR. LEMP: We don't have data on the contact lens fitting aspect of that, but it's the fact that even the patients with induced cylinder had very good visual acuities with this and indicated that their acuity as such, uncorrected, was not significantly affected, even though it's probable that some of the visual symptoms that they complained of were related to this. I don't have specific data on the rest of your question.

DR. MACSAI: Thank you.

DR. McCULLEY: Dr. Macsai, how many questions do you have?

DR. MACSAI: I have three more.

DR. McCULLEY: Okay.

DR. MACSAI: Is that okay?

DR. McCULLEY: For now.

DR. MACSAI: The next question is how does the Intacts affect the physician's ability to examine the peripheral retina of these patients, what sort of distortion is there, and can these patients have a gonioscopic examination? Can you put a three-mirror on these corneas?

MS. CROCKETT-BILLIG: I'd like to ask Dr. David Schanzlin to address that question.

DR. SCHANZLIN: Yes, the gonioscopy is not difficult to do. You do notice with the thicker rings, .35 and the other ones that we aren't discussing today, that there is a slight indentation at the 7 to 8 millimeter optical zone. You'll see a little indentation on the endothelium there, but it does not preclude visualization of the angle in these cases. Examination of the retinal periphery is also not obscured by this.

This is at a 7 millimeter optical zone. When the pupil is very widely dilated, you get an interesting

shadow when you're doing indirect ophthalmoscopy, but not something that you can't work around, so I don't think this is any significant problem for a retinal surgeon, if that's your question.

DR. MACSAI: Is the shadow eliminated when you use a contact lens?

DR. SCHANZLIN: Yes.

DR. MACSAI: There were three patients or three eyes that had the Intacts removed due to continuing undercorrection in the exchange data. Did those three eyes go on to have other refractive procedures?

MS. CROCKETT-BILLIG: This is Darlene Crockett-Billig from KeraVision. We don't have that information immediately available in terms of what the three explants or the three subjects who had exchange procedures and went on to have subsequent removals, if they had a second refractive procedure.

Dr. David Schanzlin would like to comment.

DR. SCHANZLIN: Your question was specific, but I think before someone else brought up the issue about other refractive procedures, and patients who have had removals have gone on to have PRK, patients have gone on to have LASIK procedures without complication, and the cases that at least we know about have good visual outcomes.

DR. MACSAI: The last question I have is simply

one that I found a bit confusing. Why did the sponsor change the definition of the adverse event from Phase II to Phase III regarding visual results? It made it very difficult for review of that.

MS. CROCKETT-BILLIG: This is Darlene Crockett-Billig, KeraVision. The sponsor did not change adverse event definition between Phase II and Phase III for visual symptoms or visual results. What we did is in Phase II the protocol defined a removal or an exchange procedure as an adverse event.

DR. MACSAI: Right.

MS. CROCKETT-BILLIG: And when we prepared the Phase III protocol, those were additional procedures that you would have, but they were not considered a safety-related adverse event, and that was the reason for the difference. That is our approved Phase III protocol that the trial was conducted under.

DR. MACSAI: Thank you.

DR. McCULLEY: Are you through?

DR. MACSAI: Yes.

DR. McCULLEY: That was very good, Dr. Macsai.

Dr. Middleton?

DR. MIDDLETON: Renee Middleton. I'm representing the consumer component.

Just really one follow-up, and then a specific

question. You are conceding then to the fact that you really don't have firm data with respect to your claim about suitability for additional refractive surgical procedures? That you don't have any firm data on that?

MS. CROCKETT-BILLIG: This is Darlene Crockett-Billig. I would like to call Dr. David Schanzlin to address that question.

DR. MIDDLETON: He mentioned, just in his comment there --

DR. McCULLEY: Did you have data submitted to the FDA?

MS. CROCKETT-BILLIG: No. We do not have data. It was not part of our protocol.

DR. McCULLEY: Then, as I understand it, you may not introduce new data at this point.

MS. CROCKETT-BILLIG: We do know that our patients have gone on to have other refractive surgeries. We do have that information. We can tell you what procedures they had, but we did not collect this data. This is not our information.

DR. MIDDLETON: And your comment was just for those that you're aware of, so there may be others that you're not aware of, but for the ones that you're aware of the procedures were --

MS. CROCKETT-BILLIG: Yes. Dr. Schanzlin will

elaborate on that point.

DR. McCULLEY: Based on data submitted to the FDA.

DR. SCHANZLIN: Well, we don't have data submitted. We have data here, but we don't have data submitted.

DR. ROSENTHAL: This is Dr. Rosenthal. May I say that I've written down the issue relating to the labeling regarding refractive suitability for future procedures, and we will certainly address that with the sponsor.

DR. McCULLEY: But you've received no data.

DR. ROSENTHAL: We've received no data.

DR. McCULLEY: So as I understand it, then it cannot be introduced at this time.

DR. ROSENTHAL: Right, but we have flagged it and it will be discussed with the sponsor.

DR. McCULLEY: And I think the panel has expressed its concern, and we'll probably come back to that again when we make our final recommendations.

DR. ROSENTHAL: All right. Thank you.

DR. VAN METER: Woody Van Meter. Mr. Chairman, would it be fair to ask Dr. Schanzlin to answer that question, though, that he was prepared to do?

DR. McCULLEY: If it involves introducing data

not submitted to the FDA, as I understand it, it cannot be submitted.

DR. ROSENTHAL: This is Dr. Rosenthal. I think, if I heard Dr. Schanzlin correctly, he did say that anecdotally he had reports that some refractive procedures went well, so I'm not sure you really --

DR. McCULLEY: You know, we'd all like to know, but I think this is not appropriate for these proceedings.

Dr. Middleton, did you have another question?

DR. MIDDLETON: Just a second question for my understanding. You had six eyes, I guess, that underwent exchange procedures because of the undercorrection, and I was just interested in knowing what factors play a role in undercorrection. Why might that occur?

MS. CROCKETT-BILLIG: Dr. Schanzlin, would you please address that question?

DR. SCHANZLIN: Well, recall in this study there were two phases, Phase II and Phase III studies, and if you remember the graph that I showed of the refractions of patients going into the study, clearly some of the patients with the thicker rings were beyond the performance of the product. So that automatically would bias them toward an undercorrection. The risk factors for undercorrection are primarily --

DR. MIDDLETON: In terms of the patient?

DR. SCHANZLIN: Yes. That, of course, should be better following the RPR, the recommended prescribing guidelines that we've presented today.

DR. MIDDLETON: How many of those were eye contacts or contact lenses?

DR. SCHANZLIN: How many of the patients --

DR. MIDDLETON: Did any of those wear contact lenses?

DR. SCHANZLIN: Of the ones who were undercorrected?

DR. MIDDLETON: Yes.

DR. SCHANZLIN: You mean preoperatively, before surgeries?

DR. MIDDLETON: Yes.

DR. SCHANZLIN: Can you help me with the actual number of patients that we submitted?

MS. CROCKETT-BILLIG: We have that information. We'd have to look it up. We'll get back to you on that question.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Jose Pulido. Just a quick question. Apparently, there was a difference in the number of the percentage of explants that were done at the different centers. Emory and Northwest Corneal Services had about 15 percent explantation rate versus almost half,

7 percent, explantation rates elsewhere.

Is there a big learning curve on this? Is that something that needs to be put in the labeling?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. When we analyzed the data, we looked at that as a factor, and basically I think it comes down to patient selection and making sure that you're selecting patients that are within the correct range. Our data did not indicate that there was an effect with learning curve per se.

DR. PULIDO: Jose Pulido again. I don't understand what you mean by patient selection. Conceivably, you had strict criteria that patients would be selected similarly at all the different sites.

MS. CROCKETT-BILLIG: Similarly has to do with selection of the patients in terms of are they going to be a suitable refractive surgery patient, period, or not.

Dr. Schanzlin, would you comment on that further?

DR. McCULLEY: No one-upmanship, Dr. Schanzlin.

(Laughter.)

DR. SCHANZLIN: Can you say the question again so I reformat the answer for you?

DR. PULIDO: Jose Pulido. My concern was the basically doubling of explantation rates at two centers

versus the other centers, and why should there be such a marked difference in explantation rates. Is there a problem with learning curves that needs to be put in the labeling? Why is there such a major difference between all the different centers?

DR. SCHANZLIN: I don't see it as much a problem with the surgeon having a worse result, but rather a lower threshold for having a patient who is not pleased with the result and just saying, well, we can take it out.

One of the unique things of the ring is that we can remove it, and so when patients have some of the symptoms that you've heard about today, maybe double vision at night or whatever, one of the first questions we ask clinically is, well, would you like us to take the ring out? It's really a nice decision point question for the patients, because very few of them, as you know, went on to have rings removed. The data we have today is really the data from those who selected to keep the rings in, with the exception of the removal rate cases there.

So in the cases that you're talking about there, and I don't want to go into individual surgeons, because that's really not what we should do in a study like this, but I think the surgeon involved in at least one of those two centers has a very high rate, and yet other surgeons at the same center involved in the study do not

have such a high rate. So it isn't that he had worst results. I think he had a lower threshold for removals.

But addressing the bigger concern is what is the learning curve on this? It doesn't take long to teach a surgeon to do this procedure. In fact, in the study, and I won't go into names again, one of the surgeons who came in in the latest series in the Phase III studies has data that far excels my cases, and that's perhaps more than statistical variation, or maybe it just is, but I don't think that that's a major concern based on the way you addressed the question.

DR. McCULLEY: Dr. Schanzlin, you used "I think" several times. Have you analyzed your data to demonstrate that in fact what you said you thought is in fact the case, that it's surgeon threshold, rather than any other factor? If you have not, I think that would be useful for the FDA to have.

DR. SCHANZLIN: Yes, we have. Do we have that to present or --

DR. McCULLEY: Well, you don't have to present it. You can just say that --

MS. CROCKETT-BILLIG: Yes, we have looked at it.

DR. McCULLEY: And that is indeed the case, that it's surgeon threshold that seems to be the issue in

terms of the excessive removal rate at two centers, not anything else?

MS. CROCKETT-BILLIG: That's correct.

DR. McCULLEY: Dr. Higginbotham?

DR. HIGGINBOTHAM: Dr. Eve Higginbotham, University of Maryland. Dr. Schanzlin, please stand. Thank you.

(Laughter.)

DR. HIGGINBOTHAM: Simon says.

I would like clarification of two points that are clinically related. On page 166 of your document, Table 64, it's apparent that 54 of your procedures of 449 procedures, or 12 percent, took longer than 20 minutes to perform, and I think the range went up to 44, as indicated on Table 63.

What part of that surgical time, would you say, was related to an increase in pressure when the suction cup was applied? Is it the majority, most of that surgical time, or is it still about a minute and 15 seconds, as you stated earlier?

DR. SCHANZLIN: Well, perhaps the team here can draw out the suction time data or give me a range on that.

Certainly, the first surgeries you do have longer suction times. In training surgeons elsewhere in the world, I can tell you that early surgeons tend to be

one and a half to three minutes maximum on the suction time, and I'm usually down to around a minute to a minute and a few seconds, and perhaps there are surgeons in the room that are faster than I am.

But that certainly is one of the things that is addressed in training, is the need to be cautious of that, and also to be mindful that we do raise the intraocular pressure during that process. The intraocular pressure rise, though, is not as high as with LASIK and other procedures. We don't need to raise as much vacuum on the eye, because we only need to resolve the torque of the dissection. We don't need to create a firm eye like the microkeratomes do.

DR. HIGGINBOTHAM: Thank you.

I have one more question, just a very quick question, and forgive me if this is precisely indicated in your document, but for your post-operative visual field assessment, was that a 120 screening program, as it was in the preoperative assessment?

DR. SCHANZLIN: I believe it was.

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. That is correct.

DR. HIGGINBOTHAM: So none of these patients actually underwent any full threshold or SITA testing? Is that correct?

DR. SCHANZLIN: That's correct.

DR. HIGGINBOTHAM: Okay. Thank you.

DR. McCULLEY: Just one point of clarification. You're saying that you raise the pressure with your suction range to approximately 80 millimeters of mercury?

DR. SCHANZLIN: It's approximately 80, yes.

DR. McCULLEY: That's approximately what it is in LASIK as well.

DR. SCHANZLIN: Well, I don't want to argue the LASIK data, but I believe it's much higher than that in LASIK.

DR. McCULLEY: Well, measuring with pneumotonometry with capability up to 100, I would argue with you, but we won't argue that. I just think we need to leave that maybe then out of the discussion of the comparison without solid data on either side.

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Karen Bandeen-Roche. The first part of my question I think also will go to Dr. Schanzlin, and it's a follow-up to Dr. Pulido's question, a two-part question.

So the first part is that I also noticed variation by site, and not only with explants, but in a fair variety of the outcomes of visual acuity and predictability, et cetera, so given the range of outcomes

in which there was variability by site, does your answer still stand that there is good data to support that that's selection, rather than learning curve?

DR. SCHANZLIN: I think so. Perhaps this is really a statistical question. Are the sites poolable? And I think that there is no data that suggests that we could exclude any one site, because they really are not that different. It's only when you look at the results. That's why that statistically -- you know, I think you have to consider the group as a whole, and not worry whether one surgeon that has done 200 of these has a little bit better data than somebody who's done just a few. I don't think that there's a difference to that degree.

DR. BANDEEN-ROCHE: I would comment that poolability analyses do have fairly low power often, and so really large differences would be needed to fail that analysis.

The second part of my question I think is related, and it's just an analysis question. Were any of the analyses done to determine P values or confidence intervals that took into account the clustering within sites or within positions, the effect of which would be to decrease precision?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. I'd like one of our statisticians to answer

that question, please. Don Young will answer that question for us.

MR. YOUNG: Don Young, San Jose State University. I am consultant to KeraVision. I have no equity interest.

With regard to your question on whether or not there was any clustering correction or adjustment, no, there wasn't. We did not do any of those techniques.

DR. McCULLEY: I think Dr. Sugar was the person I was aware of next.

DR. SUGAR: Two unrelated questions. First, concerning specular microscopy, in the analysis of the patients with the greater cell losses, was there a sense in looking at the photographs, videotapes, or whatever you had that there was cell loss that was emanating from the point of flexure of the posterior cornea, Descemet's membrane, and would this suggest the possibility of ongoing cell loss in the deeper implants or the thicker implants?

I guess Dr. Edelhauser, or I'm not sure who would be the person to answer.

MS. CROCKETT-BILLIG: I'd like to call Dr. Edelhauser, please, to address that question.

DR. EDELHAUSER: Dr. Edelhauser, Emory University, consultant and reading center for specular microscopy for KeraVision.

The specular that we performed was with the non-contact Robo, and indeed, getting the peripheral 10 o'clock reading was probably the most difficult reading to get, because the image sometimes would be adjacent to the ring, and most of the speculars that we analyzed had between 70 and 150 cells, but indeed you could see in the image that came up on the Robo that in that peripheral region there could be a dark area where some of the cells could be missing that we could not read. So the chances of variation in the 10 o'clock region would be much greater than, say, central.

DR. SUGAR: Variation in accuracy of your capturing data or variation in cell density?

DR. EDELHAUSER: Well, we were masked when we read this. I would say that our accuracy, when we analyzed it, we looked at it in terms of -- well, I didn't do the analysis. We sent the data there, but when we analyzed on the Robo, you touched the center of each one of these cells, and to get a maximum of 70 to 150 cells, so I would say what cells showed up were as accurate as the instrument could provide.

DR. SUGAR: And did you have a sense, even with the later analyses, that there were cells that were different in that area?

DR. EDELHAUSER: I would say no. The cells

looked the same in terms of what we saw on the Robo. The percent hexagons were the same and the coefficient of variation were the same.

DR. SUGAR: Thank you.

DR. McCULLEY: Were there more dark spots that you couldn't interpret?

DR. EDELHAUSER: Well, the dark spots were particularly off in the periphery, whereas in the central reading, because this instrument will seek the apex of the cornea, you were always right on the money at all times.

DR. McCULLEY: Any other questions for Dr. Edelhauser while he's at the podium?

(No response.)

DR. McCULLEY: Thank you.

Dr. Sugar, you had a second question?

MS. CROCKETT-BILLIG: Dr. Holladay wanted to make a comment.

DR. HOLLADAY: Jack Holladay, consultant to KeraVision. The one comment I wanted to make about that, we used the Robo also, and what you have to realize is when it takes a measurement, the endothelial surface has to be almost flat over the area that the reflection comes from in order for you to be able to see all the cells in focus, because it's in one focal plane, but what happens is when the plastic is in the cornea, that indentation of the back

surface where there are endothelial cells makes it impossible for that particular endothelial camera to get that entire plane in focus.

So what he's talking about is that you can see one portion of that plane and those cells look the same, and then where it begins to bend off it gets dark and you can't see anything. So the only indication we have is that cells in the area that you can see are normal.

The second aspect is that the 10 o'clock that you measure preop, post-op has to be right inside the ring, so the chances of hitting the same point pre and post-op are very difficult to do, and that's why I think you're seeing this variation. It doesn't have anything to do with the cells.

DR. SUGAR: Thank you.

The other question I have is about surgeon education. You presented in your package what the program would be, and I'm just trying to verify that surgeons would be required before receiving the product to take the course.

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. Yes, that is correct.

DR. SUGAR: Thank you.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: Yes. This is Mark Bullimore.

I've heard a lot of data presented on visual acuity and a lot of different sort of slices and dices done. My question is this. When you compare the best spectacle-corrected visual acuity pre and post, and you had a table in your presentation, and you can probably find it quicker than me, but what I want to know is what is the mean change in best spectacle-corrected visual acuity in terms of number of letters? You alluded that there's a change in the distribution, but when you've quantized the data in terms of lines of visual acuity, it's not immediately obvious to me what that might be. So that's one thing I'd like to know.

The other thing is, in terms of the induced cylinder, I can't remember what type of astigmatism is being induced by the procedure. Are we introducing a with the rule or against the rule astigmatism or have we got a shotgun effect? Is the sort of astigmatism usually this way or this way? I feel like the Pope now.

(Laughter.)

DR. BULLIMORE: But given the construction of the device, I would have thought you'd get some trends occurring.

So take those questions in either order you would like them.

DR. McCULLEY: And I had one, too, that really

fits right in with that. What was the association of the induction of cylinder relative to the 30 degree gap and relative to the segment? Which is what you were saying, too.

DR. BULLIMORE: You said it more eloquently.

DR. McCULLEY: I didn't have to cross anybody, though.

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. In regards to Dr. Bullimore's first question comparing what was the mean change for BSCVA, for both protocols for the PMA cohort the main change was 0.3 lines, plus or minus 0.83 lines.

DR. BULLIMORE: Sorry. Say that again.

MS. CROCKETT-BILLIG: A 0.13 line change.

DR. BULLIMORE: It's 0.13 line. So that's just under one letter, basically, translating it.

MS. CROCKETT-BILLIG: Yes.

DR. BULLIMORE: And that would be consistent with a magnification effect that you might anticipate with the change of the refractive correction moving from the spectacle plane to the corneal plane, so one could explain the change in best spectacle-corrected visual acuity almost entirely on the basis of a magnification effect without even considering what the optical effects of the procedure might be.

What about the axis of cylinder? Have we got that?

MS. CROCKETT-BILLIG: I'd like Dr. Holladay to address that question.

DR. HOLLADAY: Jack Holladay, Houston, Texas, consultant. You're absolutely right. We would expect for the average correction to effect a one letter magnification, so for the overall cohort, with everyone mixed together, you didn't see any significant change from pre to post-op when you took all of the patients. The point was there was a subgroup of those, though, in which there were 20 percent that had more than a one line change, which was statistically significant at a very small P value.

The point was that that number we think is a good number. The ones that decreased we also knew could go down as many lines as you wanted to because they weren't up at the upper end. As you saw, three of the four patients that dropped lines were 20/12, so we believe that there is a claim for 20 percent of the patients, which we can't predict, that actually can have a statistically significant improvement in one line in vision.

In terms of the whole cohort of the 494, there is no difference between the pre and the post-operative value. So all we'd like to do, if it's possible, is

mention that there may be a group of patients who actually do have a one line improvement in their vision.

DR. BULLIMORE: I guess I have the same problem with that statement that the reviewers seemed to have, and that is, you know, you can't say that when you have an average variable change that some people got worse and some people got better, and then really just choose to ignore the people who got worse. I mean, that's just sort of statistics that we expect to come from inside the Beltway and not from this part of the country.

(Laughter.)

DR. BULLIMORE: I accept your statement that some people did get better and I accept the statement that some people get worse, but I'd like to sort of look at the distribution of the whole, and the .13 lines seem to me to be a bit much better indication in terms of what's happening to the sample as a whole and what is the most likely thing that's going to happen to a patient that I would refer or, were that patient me, what would be my expectations of my own vision. So that's the only point I want to make.

What about the axis of cylinder? Have you got some data on that?

DR. HOLLADAY: Can I make one other comment about that in response?

DR. McCULLEY: Well, I think that this is an important point, yes, and I think let's stay on it until maybe anyone else that has comments about it as well, because I think one thing that we should have learned over the years, if we don't make our advisory panel opinion clear, then we don't have the effectiveness that we're being asked to provide.

DR. HOLLADAY: I don't disagree with any of those comments at all. As a matter of fact, to pick a subgroup and to say that they are statistically significant, although you can't predict who those are, is certainly a good point.

The only reason I raise that is I've been involved with several other PMAs that come from other refractive procedures, but that we've never seen any numbers in which anyone has ever had an improvement in visual acuities in a small percentage, and that's the only reason we brought that up.

DR. BULLIMORE: The claim's not been made, I believe, in terms of the things that were presented to me in the literature, the claim's not been made with reference to other refractive surgery procedures. The claim has been made with respect to other corrective technologies, such as spectacles and contact lenses, and the data doesn't support that claim, based on the fact that you've only got a .13

line or less than a letter change in visual acuity. So that's really what I'm speaking to. I'm not wanting to compare it to anything else. I just want to get the data straight.

DR. McCULLEY: And their study was not done to compare, so that's an inappropriate line of reasoning for these discussions.

Karen?

DR. HOLLADAY: The cylinder issue --

DR. McCULLEY: We'll come back to it. We're still on this enhanced acuity issue.

DR. BANDEEN-ROCHE: Yes, Karen Bandeen-Roche. My follow-up question would be that as far as I understand, a one line change in acuity is fairly constant with the measurement error associated with visual acuity, and from Dr. Sugar's report there was approximately -- I mean, slightly less, but not a very different percentage who declined by one letter as who improved by one letter.

So my question would be what is the evidence that the hyperacuity phenomenon represents something other than what would be expected by the measurement error of the procedure?

DR. McCULLEY: Would sponsor like to respond to that or let the comment stand?

MS. CROCKETT-BILLIG: One moment, please.

We're getting information together.

DR. McCULLEY: I'm sorry, sponsor. We really need for you to come forward.

MS. CROCKETT-BILLIG: All right. What we found was that we found 19.5 percent of our subjects did have an increase in their BSCVA of five or more letters or one or more lines. That's what our analysis showed. We have the P value. We found that the increase in BSCVA was statistically significant and with a P value of 0.002.

DR. McCULLEY: Do you have comments relative to those that were just made in criticism of your approach to this?

MS. CROCKETT-BILLIG: I'd like Dr. Chiacchierini to address that comment, our consulting statistician.

DR. CHIACCHIERINI: Yes, I am Dr. Richard Chiacchierini. I was the former director of the Division of Statistics in the Center for Devices and Radiological Health. I'm now the vice president of statistical services at C.L. MacIntosh & Associates. I have no financial interest in the company other than my consulting fee.

The whole issue of determination of whether or not something is within sampling variation is the precise nature of statistical testing. The fact that we have a statistically significant improvement is beyond doubt.

There is a statistically significant improvement.

The issue before this body is whether that is a clinically important improvement, so I think what we need to do is distinguish between statistical significance, because had this been in the sampling error of the distribution, it would not have been statistically significant. It was in fact statistically significant.

Now, the fact is, is this a clinically important improvement? That is, a one line increase? That I think is what we're discussing.

DR. BANDEEN-ROCHE: This is Karen Bandeen-Roche. If I could just ask for a clarification, could you please just remind us exactly what was the test for which you're quoting statistical significance? I don't mean the method, but what was the denominator, what was being compared, et cetera? Just refresh our memory on that, please.

DR. McCULLEY: While we're waiting for sponsor to pull a response together, just a point of clarification for us. In the past, we have taken two lines as being clinically significant in our guidance documents and in our discussions. Whether that's appropriate or not, that has been our tendency and we're talking about one line, not two lines, here. So if the issue is clinical significance and that's your argument, then we have taken two lines in the

past as being clinically significant.

DR. CHIACCHIERINI: The line change denominator was based on 410 patients.

DR. McCULLEY: Do you have a response to that, Karen?

DR. BANDEEN-ROCHE: No, although, as I understand it, that's mean change? Mean change. So I think combining Dr. Bullimore's and my comments, I wouldn't change my comment.

DR. CHIACCHIERINI: It would be the median change. It was a non-parametric test.

DR. McCULLEY: Your comments still stand? And would you state clearly for us what your view on this is, so that we're real clear?

DR. BANDEEN-ROCHE: Well, my view is that in terms of the percentage with improved visual acuity, not the median change, but the percentage with a line or more visual acuity improvement, I am not convinced that it's beyond what would be expected by measurement error of the procedure.

DR. McCULLEY: Dr. Macsai?

DR. MACSAI: Since we're discussing this issue, Dr. McCulley, I would like to bring again to the panel's attention and to the sponsor's attention that we not compare apples with oranges. We do not have the best

corrected visual acuity on these patients preop. Their best corrected visual acuity would be in a rigid, gas-permeable contact lens, not a spectacle.

So you don't know for sure, statistically significant or not, whether this is of any significance clinically to the patient, and I think it would be inappropriate to make a statement as such, because you need to know what their best corrected visual acuity is preop if you are going to say that post-op they have had an enhancement or improvement of their best corrected visual acuity.

DR. McCULLEY: Okay. We're still on this point, prior to coming back to the astigmatism question that Dr. Bullimore raised. Are there other questions on this issue? Dr. Wang?

DR. WANG: Ming Wang. I'd like to second Dr. Joel Sugar's comment about lack of masking of the possibility of enhanced visual acuity of the unoperated eye. It's relevant to the hyperacuity issue.

DR. McCULLEY: I think that the panel seems to have a fairly consistent opinion relative to that issue. Can we now go to Dr. Bullimore's question about astigmatism gap segment, et cetera?

MS. CROCKETT-BILLIG: Yes. Dr. Bullimore, would you repeat that other question to make sure I have it

right?

DR. BULLIMORE: Yes. I seem to remember somewhere in the materials I was sent the fact that the main or maybe the median surgically induced change in refractive -- or surgically induced change in cylinder, whatever the appropriate term is -- was on the order of half a diopter. My question was is that randomly distributed or was there a tendency for it to be, say, with the rule or against the rule, clustered around a certain meridian?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. The induced cylinder that we did have was primarily with the rule cylinder.

DR. BULLIMORE: I guess, as a follow-up to that, and this is a question as much for the panel as the sponsor, is that information that would be useful to have in the labeling? For example, were a patient to present with astigmatism at axis 180, one might counsel them differently than if they had astigmatism at axis 90. I'll leave that for discussion later.

DR. McCULLEY: Other comments in that regard? Dr. Macsai?

DR. MACSAI: Does the sponsor have any data as to whether or not induced astigmatism was orthogonal or non-orthogonal -- i.e., regular or irregular -- in light of

the visual symptoms represented by some of the recipients of the device?

MS. CROCKETT-BILLIG: I'd like Dr. Schanzlin to answer that question, please.

DR. SCHANZLIN: Dr. Schanzlin. It's primarily orthogonal. That is, when you refract these patients, they're easily correctable with spectacles.

DR. McCULLEY: Other comments? Dr. Jurkus?

DR. JURKUS: This is Dr. Jurkus. I had a question regarding a number of patients who reported difficulties with night driving, halos, and glare, and they were then treated with pilocarpine, and then if I read the table correctly in Volume 3, that treatment was then discontinued. I was wondering if you could give any information regarding what their subjective symptoms were after the discontinuation of pilocarpine.

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. The patients primarily went back to where they were prior to treatment with pilocarpine; i.e., the treatment really wasn't effective in reducing the visual symptoms for most subjects.

DR. McCULLEY: Dr. Matoba?

DR. MATOBA: Alice Matoba. I had a question about the 34 patients in whom you have removed the implants. Fourteen were because they were dissatisfied

with their vision and 16 because they had visual symptoms with which they were dissatisfied. Were those numbers excluded from your final analysis, the 449 patients for whom you've given us the data? And if so, how would you justify excluding them?

MS. CROCKETT-BILLIG: The 449 subjects were included in the safety analysis. We had 449 implants for safety.

DR. MATOBA: But did you exclude the 34 in whom you removed the implants? They're not included in the 449, is that correct?

MS. CROCKETT-BILLIG: At month 12, we had 410 subjects, and they were not included in that information, but they were part of the overall safety of the 449.

DR. MATOBA: Overall safety, but not patient satisfaction, for example.

MS. CROCKETT-BILLIG: They didn't have an implant at month 12 to have the patient to take the survey.

DR. MATOBA: Right, but somehow it doesn't seem valid to just drop them out of analysis, since they weren't satisfied.

MS. CROCKETT-BILLIG: We did an alternate analysis, a carry forward analysis, where we looked at all subjects, carrying them through the whole time period as if they would have been in the trial for the whole 12 months,

and I'd like Don Young to address that question.

MR. YOUNG: Don Young, San Jose State. As Darlene has mentioned earlier, we did a carry forward analysis on all patients if they dropped out of the cohort because of removals and the various other things that you've cited, and those results are presented in the appendix to the cohort report. Looking at the differences in the results, there are no substantial differences in the results.

DR. MATOBA: Did you look at the different sizes? For example, the majority of those patients, 56 percent, had the .35 millimeter implant. If you looked at different sizes of implants, was there still no significant difference if you subdivided and categorized the data?

MR. YOUNG: As far as I can recall, there was no difference.

DR. McCULLEY: So your efficacy data did not include the 34.

MS. CROCKETT-BILLIG: That's correct.

DR. McCULLEY: Your safety data did.

MS. CROCKETT-BILLIG: That's correct.

DR. McCULLEY: So there has to be clear labeling that in the efficacy data that includes an additional 4.7 percent explant rate.

Dr. Macsai?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig, KeraVision. Only 20 eyes were explanted at the month 12 time period, though.

DR. MACSAI: This is Dr. Macsai. I'm a little bit confused. In comparing visual symptoms that are often or always mentioned by these patients, in my previous comment to you talking about pupil size, mesopic, and in my discussion with Dr. Lemp regarding halos, double images, and fluctuating distance vision, those percentages or those increases -- let's just take halos, preop, one out of 357 patients, .3 percent. Post-op, 39 out of 328, 11.8 percent, a 37 times increase in often/always complaints of halos, not a variation with pupil size.

Is 39 out of 328 accurate if you have excluded the dissatisfied patients, the 16 with visual symptoms that caused explantation? Should that numerator in fact be 55?

MS. CROCKETT-BILLIG: We didn't do the analysis in that fashion in the data that we submitted. Now, we could certainly go back and look at that.

DR. McCULLEY: I'm a little confused, too. This is McCulley. Your symptom percentage does not include those patients who were sufficiently symptomatic to have explant.

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. Our symptom percentage was based on the subjects that had

the implants at month 12. There were 20 subjects who had removals prior to month 12, and those subjects would not be in that specific N for visual symptoms at month 12.

DR. McCULLEY: So we just have to be very careful about making sure that when the final statistics are done that the percentages that are presented by one mechanism or another make it clear that there are those that had the symptoms that still had the implant and those that had the symptoms that were so severe that they had the implant removed, so that those numbers don't misrepresent.

Dr. Wang?

DR. WANG: Ming Wang. I just have a quick comment and a question for the sponsor. The comment's about the .35 grouping possibly needing to be treated separately in response to Dr. Rosenthal. I think probably it will be more than philosophical, in that Dr. Sugar, Dr. Grimmett, and Dr. Van Meter have all mentioned incidences of possible separate labeling needing for that size.

I'm concerned about the doubling of problems in that size compared with other sizes. For example, diplopia, 15.3 versus 6.9 percent. So are we hitting a point of nonlinearity in which that size may present a problem physiological to the cornea?

My question to the sponsor is is there any stratification -- this is sort of related to Dr. Matoba's

question -- of explant rate and complications according to size?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. We have looked at the explant rate according to size, and we're pulling the information up.

DR. McCULLEY: I think that was presented, wasn't it? That's already been presented. I think we'll deal with that. Your points are very good, but I think in the normal proceedings of the panel we'll deal with those issues when we come to labeling recommendations. Does the FDA need anything? I think we can deal with it. The issue's real and valid, and it will be dealt with when we deal with labeling issues. It really doesn't require a response from sponsor at this time.

Dr. Grimmett?

DR. GRIMMETT: Dr. Michael Grimmett. I wasn't here on the panel when your protocol was designed and developed, so this is a background question. When the testing was selected at a 7 millimeter pupil for the mesopic testing, how did you all choose 7 millimeters as your target pupil size and did you analyze the data for 6 millimeters, for example, or that just wasn't the way it was done, and did you take into account the Stiles-Crawford effect and other issues like that?

MS. CROCKETT-BILLIG: I'd like Dr. Schanzlin to

answer that question, please.

DR. SCHANZLIN: We just did the cutoff at 7 because that's the optical zone where the ring comes into effect, so when we were designing this, we were looking mainly at what is the visualization of the ring. If you have someone whose pupil would dilate to 9, they might actually see the shadow of the ring, so that was why we looked at that cutoff.

DR. GRIMMETT: As I recall in George Waring's lengthy book on RK, due to the Stiles-Crawford effect, under scotopic conditions the effective pupil size was approximately 5.5 or something like that.

I was just interested in how 7 was chosen. It was just due to the physical dimension.

DR. SCHANZLIN: It was physical dimension of the implant.

DR. HOLLADAY: Jack Holladay. I wrote that chapter for George.

(Laughter.)

DR. HOLLADAY: And it's true that when everything's open -- and that goes all the way back. I don't want George to get credit for that either. It goes all the way back to Stiles and Crawford, and it just shows that when you actually do take into the Stiles-Crawford effect that anything beyond a 5.5 millimeter size pupil has

no input or any light intensity that forms the main image on the macula.

It doesn't, however, relate to peripheral images, shadows, and other things that you see. So the 7 millimeter choice was just specifically to see whether it was inside or out of the ring, but there's nothing magic about that 5.5 millimeter, other than when you get bigger than that the contribution to the macular image is small, but it still forms a lot of peripheral images, and that's why we do those, to see if there's peripheral glare or unwanted images. That's the reason.

DR. GRIMMETT: Thank you.

DR. McCULLEY: Are there other questions from the panel? I have two. One is, you presented no information on topography.

DR. SUGAR: Yes, they did.

DR. McCULLEY: They did?

DR. SUGAR: It wasn't presented today, but it's in there.

MS. CROCKETT-BILLIG: Yes, the information is in the panel package.

DR. McCULLEY: Okay. Well, my problem with topography has been interpretation of it, so I guess my question then is, not having reviewed that specific hard copy, can you give us a summary of what your topographical

analysis showed?

MS. CROCKETT-BILLIG: Yes. I would like Dr. Holladay to address that. He's independently reviewed our topography.

DR. BULLIMORE: Can we have Dr. Waring?

(Laughter.)

DR. McCULLEY: Jack, I know you love this stuff. Just bottom line.

DR. HOLLADAY: Can we show a slide?

DR. McCULLEY: A slide? A slide you can show me and everyone else.

DR. HOLLADAY: Well, let me just tell you, rather than showing you, because we're all getting late in the day anyway, but I'll tell you this. The topography data pretty much helped us correlate exactly with what the vision data was, and that was this. We saw the same predicted corneal acuity changes on the topography as we saw in the regular data, and we saw a very high correlation between the changes in those two, meaning this, that about 97 percent of the corneas preoperatively were at the optical limit at 20/10. Post-operatively, that dropped down to about 94 or 95 percent at 20/12 and 20/16, the same sorts of things that we saw in the visual acuity change.

Again, the with the rule astigmatism that was seen showed up on the topography also, and the aspheric

changes that we saw, both in the quantitative maps and on the surfaces, showed up, too. So what it did is it helped -- and that's why I was kind of interested in that enhanced acuity. When you get more prolate, sometimes you can get better optical images and we were unable to correlate those in terms of proving that those were the patients that got better, so that fell through, but the fact is every topographic change in terms of quality, shape, and astigmatism and aspheric change paralleled exactly what their data showed in terms of visual acuity.

Any other specific questions about that?

DR. McCULLEY: Are there any others? Karen?

DR. BANDEEN-ROCHE: Karen Bandeen-Roche. I had a few more specific questions. Hopefully, they shouldn't take very long.

The first one goes to patient satisfaction. I was curious. Of those patients who had a good contralateral candidate eye, what was the percentage that actually opted to have the other one implanted?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. We'll pull that information for you.

DR. BANDEEN-ROCHE: Okay. The second one is very quick. It goes to the rate of having a removal. Are you fairly satisfied that that has stabilized or are there yet patients who might yet opt to have their ring removed

in a reasonable expectation?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. Yes, we feel the removal rate has stabilized. Actually, we encouraged the patients, even though they were unhappy, to stay in the trial for at least six months to see if their situation would stabilize over time. So we feel that the information is accurate and, again, that is stabilized.

DR. BANDEEN-ROCHE: Thank you.

The third question goes to data for corneal sensation. I believe in six months there were 259 patients evaluated. At 12 months, that had dropped to 237. So my question is is there association between corneal sensation and those who dropped out? In other words, are we possibly masking a higher loss of corneal sensation from those who weren't evaluated?

MS. CROCKETT-BILLIG: Darlene Crockett-Billig. No, that is not the case.

DR. McCULLEY: Dr. Wang?

DR. WANG: Ming Wang. You have reported adverse events, such as anterior chamber perforation, function decrease of two lines, and also shallow implant segment removed. I was wondering, is there any association of these complications with the experience of the surgeon? It would be important for me as a surgeon to know that perhaps these complications are less likely once one is

well trained, if it's indeed offered to the general public and to all surgeons.

MS. CROCKETT-BILLIG: I would like to ask Dr. Schanzlin to address that comment.

DR. SCHANZLIN: I think properly trained these are easily addressed. Certainly, the perforations we talked about earlier, that's certainly an issue of just how to set a diamond knife blade.

At least one surgeon, one where the shallow implant was there, it was a shallow incision to start with, and if you look at what happens when you do a shallow incision and try and make the dissection, you get a lot of resistance. You can easily learn that when you see a wave in front of the advancing dissector and you're struggling to advance it, that means you're too shallow, so you should back off and you can rechannel deeper and get a deeper incision.

The other thing is that if you see post-operatively that the ring on day 1 is at less than 50 percent depth, that's the time to intervene, not wait six months like we do in trials and see what happens.

So these are things that certainly can be addressed in training that can only improve the results, I believe.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Jose Pulido. We know that with radial keratotomy there is inherent instability of the cornea with altitude and there is a decrease in the tensile strength of the cornea. Do those things exist with this implant?

DR. McCULLEY: Dr. Schanzlin?

DR. SCHANZLIN: Well, there a couple of things in RK that we're concerned about. One is what happens with altitude, and our patients have traveled in airplanes. I don't have anyone that's been to Mount Everest yet, but certainly going up in planes to that equivalent, 8,000 feet, and also on the West Coast, people doing a lot of skin diving, it doesn't seem to cause fluctuations in vision based on that.

The other large concern, of course, is what happens with time with this, and we've closely looked at the data to look at what happens. Is there any drift, hyperopic drift, over time? It seems like it's very stable, three months, six months, nine months, 12 months. So I don't anticipate we have a danger there.

DR. McCULLEY: Dr. Higginbotham?

DR. HIGGINBOTHAM: Dr. Eve Higginbotham. A similar question, Dr. Schanzlin. We have seen changes in refraction in women that are perimenopausal and post-menopausal. Did you analyze the data for those factors in

terms of the women?

DR. SCHANZLIN: Yes, we did, and am I right in saying that there was no difference between males or females, no difference between females premenopausal or post-menopausal? That's true.

DR. McCULLEY: I think this last question that I have, Dr. Schanzlin, would be most likely for you as well. You mentioned that there was localized staining in 4 to 7 percent of patients at various time points. Where was that located on the cornea? Was there a pattern or was it random?

DR. SCHANZLIN: Well, the 4 percent, of course, you're talking about the pooled data and it's pretty much random, usually at the limbus, 7 o'clock and 5 o'clock, close to the limbus.

DR. McCULLEY: Outside the ring.

DR. SCHANZLIN: Outside the ring.

DR. McCULLEY: So none in the center that you specifically commented on? Again, getting back to the question of any adverse effect from the decrease in corneal sensation, have you looked at the central corneal epithelium with specular confocal to try to determine whether it's healthy or not?

DR. SCHANZLIN: We have not and certainly have not submitted that. I believe Penny Aspell presented, I

think it was at CLEO, some time ago looking at ultrasonic microscopy of epithelial thickness close to the ring centrally, and I believe, if I recall, the conclusion was that there was a mild thickening of the epithelium just inside of the ring, but again, she's not here to present that data and we did not submit it. It's a one-center study that has not been verified anywhere else.

DR. McCULLEY: Okay. Thank you.

Any other questions from the panel before we break for lunch?

(No response.)

DR. McCULLEY: Seeing none, Ms. Thornton has a couple of comments, and then we're going to take a one-hour lunch break.

MS. THORNTON: I'd like to announce that the lunch for the panel will be in Room 20H just down the hall. That room has been reserved for panel and for FDA. The sponsor has Room 20G, which has been reserved for their lunch.

Please take with you your cups, your cans, your paper products, and deposit them in the rubbish bins just outside the door at the request of the management.

Thank you.

(Whereupon, at 12:26 p.m., the meeting was recessed for lunch, to reconvene at 1:26 p.m.)

AFTERNOON SESSION (1:40 p.m.)

DR. McCULLEY: Can I ask everyone please to take your seats? Let me ask the panel just for a general feel. Do we want to have open discussion and then go to the questions, or do we want to incorporate our discussion in the questions? In the questions. There seems to be strong sentiment for that.

Do you guys want to project your questions, FDA? Malvina? I'll start reading the first question.

"Do the outcomes of the endothelial cell density analysis presented in this PMA provide reasonable assurance of safety for all three thicknesses of the ICRS? What, if any, additional data are needed to make this decision?"

I think the primary reviewers seemed to have a pretty consistent feel about this. Joel, can I ask you to open discussion?

DR. SUGAR: I think all three of our reviews suggested that some further analysis of the patients that have had difficulties, especially those who had 0.35 rings, ought to be obtained, further longitudinal data.

DR. McCULLEY: So postmarket study. Is that the appropriate word? We have to be careful in terms of the words. So it's postmarket study.

Dr. Grimmett, do you have anything further to

add to that? I think there was consensus.

DR. GRIMMETT: Dr. Grimmett. I echo those comments.

DR. McCULLEY: Does anyone disagree with that?

(No response.)

DR. McCULLEY: Okay. My impression is that if we are going to request that, that it is advantageous for us to be as specific and narrow in our recommendation as possible, not make an open-ended recommendation. Does anyone have a specific recommendation as to how one would like to see the study carried out?

Dr. Sugar?

DR. SUGAR: Sugar. I would like to see on the patients who had -- I don't want to use the term "significant" -- on patients who had cell losses in the 10 percent range, peripheral or central, that further data be obtained on those patients, if possible. Also, that prospectively -- and I don't know how to get specific with this, but that a subset of future patients receiving the 0.35 ICRS have endothelial data obtained on them.

DR. McCULLEY: Okay. I gave some thought to the specificness of it, and it's in the same vein as what you've stated. It's that we request two-year follow-up on the patients that have had 10 percent or more cell loss. What we have as our controls in that are going to be the

other two size rings, that a comparable number of patients, a matched number of patients with the 0.25 and 0.30 ring be done as well as the control, because that's our comparison, and that we request an additional 25 patients with the 0.35 ring for future study, starting from preop through two years.

Dr. Higginbotham?

DR. HIGGINBOTHAM: Eve Higginbotham. Would you also specify from the same site, considering our previous discussion about site differences in outcome?

DR. McCULLEY: I wouldn't have a problem with that. Well, I'm not sure that you really want same site, because we want real world. I think let's leave that -- I would suggest we leave that detail out.

DR. HIGGINBOTHAM: I'm suggesting a set of case-controls from the same site as the patients --

DR. McCULLEY: For the prospective patients.

DR. HIGGINBOTHAM: Exactly.

DR. McCULLEY: Because the others are already scattered, presumably, among more than one site. Okay, I think that's reasonable.

Marian?

DR. MACSAI: Dr. McCulley, I'm not certain what number of patients are needed in each group to ascertain statistical significance in endothelial cell loss, so I

question why we would just randomly ask for 25 more. Perhaps someone from the agency, such as Dr. Eydelman or Dr. Boulware, could help me out here?

DR. McCULLEY: Recommend a number that would give us some degree of confidence? Okay. So instead of saying a specific 25, a number of patients to be studied prospectively that will give us a statistical degree of comfort.

DR. MACSAI: To detect what?

DR. McCULLEY: I know you two were talking at the time. Did you hear what I said?

DR. EYDELMAN: Part of it.

DR. MACSAI: I would think what we would be interested in is a greater than 6 percent cell loss rate in the periphery, greater than that found by Bourne in the normal --

DR. McCULLEY: Bourne was 0.6 centrally. Again, what I suggested was a 0.25, a 0.30, and a 0.35 as the control, the first two for control relative to the 0.35, which is the one that is carrying our significant concern, and we will assume that there's -- I mean, that's making the assumption that there is not a significant change in the 0.25 and 0.30. But we can't ask them to define what happens in the normal population in --

DR. MACSAI: Right, I understand.

DR. McCULLEY: So I think that's putting too much on them. But I think if the prospective study is statistically -- the sample size is statistically determined with the three ring diameters --

DR. MACSAI: The sample size may already be there. Excuse me, Dr. Macsai. The sample size may already be enrolled. They may not need to enroll more patients.

DR. McCULLEY: Marian, what I said --

DR. MACSAI: That's what I'm trying to say.

DR. McCULLEY: There were two parts to the suggestion. There are those that have demonstrated significant cell loss to date, that they be followed to two years. That data is submitted.

DR. MACSAI: Yes.

DR. McCULLEY: That sample size is predetermined. That a to-be-determined sample size for each of the three ring sizes be prospectively enrolled from preop through a to-be-determined length of time additionally to support whether there is endothelial cell loss in the periphery or not.

DR. MACSAI: I guess I don't understand the second part of that recommendation. If they have three groups, they've done endothelial cell counts that have been monitored by a central unit for 0.25, 0.30, 0.35 millimeters. Why not just follow those patients out

longitudinally?

DR. McCULLEY: If that sample size would give statistical significance, then I think that would be reasonable. If it won't, then I would request the prospective study. I was anticipating that that sample size would be very difficult to get statistical significance on.

DR. EYDELMAN: Dr. Eydelman. Panel would need to help us specify the difference that you're trying to detect as to the percent loss between 0.35 and 0.30 and 0.25 rings, because we have done statistics previously in order to establish a 10 percent loss, and you need at least 80 eyes. So just comparison of the groups, we need another variable to detect the sample size -- i.e., different within what percentage? What would be your equivalency threshold between the two endothelial cell populations?

DR. McCULLEY: You mean a percentage greater than?

DR. EYDELMAN: Yes.

DR. McCULLEY: Well, we've talked about the variability of specular before, and the 10 percent has been the number.

DR. EYDELMAN: So 10 percent over what length of follow-up for the second group? I understand for the first group you want two years. What length for the second

group?

DR. McCULLEY: Is the sample size large enough as it exists if followed to two years to give statistical confidence as to whether there is a progressive loss or not? That's a question.

DR. EYDELMAN: Progressive loss of what magnitude?

DR. McCULLEY: Greater than 10 percent. Ten percent or greater.

DR. EYDELMAN: Progressive 10 percent over what period of time?

DR. McCULLEY: Two years.

DR. EYDELMAN: Yes. If you follow the same sample as they have currently for two years as opposed to one year, they were able to determine that there was no loss of 10 percent at one year.

DR. McCULLEY: Okay. So the recommendation could be as specific as following the current population that have lost more than 10 percent for two years, for a total of two years data gathering.

DR. EYDELMAN: That's the first part of your recommendation. And the second part?

DR. McCULLEY: Well, the second part, again, may need to drop. If you can reach a reasonable degree of comfort one way or the other with the current sample size,

then I don't think the second part is necessary. If you can't, then I think that the second part will help.

Dr. Pulido?

DR. PULIDO: How about looking at all the enrolled patients in the 0.35 millimeter group over the two years and comparing that to a randomly selected group from the 0.30 and 0.25 millimeters over the same two-year length of time?

DR. McCULLEY: I thought I had a better suggestion than you. I clearly didn't. So I think that sounds reasonable as well.

DR. MACSAI: Dr. McCulley?

DR. McCULLEY: Yes, Dr. Macsai.

DR. MACSAI: We've spoken many times that these patients who have refractive surgery frequently have preoperatively worn contact lenses, and upon cessation of their contact lenses they realize an increase in their endothelial cell count. So perhaps, in fact, you would have to stratify that data to clarify pre-Intact implantation contact lens wear and not.

DR. McCULLEY: They did that before, and I would assume that they would continue to do that.

DR. MACSAI: But to make sure that those groups were large enough for statistical validity.

DR. McCULLEY: Matched appropriately.

Is that specific enough for you? I mean, I'm not sure we got it nailed.

DR. EYDELMAN: Neither am I.

DR. McCULLEY: So you need more help?

DR. EYDELMAN: If you can.

DR. McCULLEY: Yes, Marcia.

DR. YAROSS: Marcia Yaross. I would suggest that the sponsor be given an opportunity to demonstrate that by postapproval follow-up of the existing enrolled population, they can make the case for determining, with adequate statistical significance, that there is no safety issue before they be asked to enroll additional prospective subjects.

DR. McCULLEY: Okay, that's well stated. I mean, that was, in effect, the intent. That's better stated. That's the general comment, but then that leaves it for FDA and sponsor to determine exactly who is going to be looked at. I think for how long, we're saying two years at a minimum. And whether you're going to take all of the 0.35 group or whether you're going to take the 0.35 group that's had 10 percent or greater loss, get a matched group in the 0.25 and 0.30, I guess we really didn't hit that, although there's no reason you can't do both. It could be a two-pronged study. You could take all of the 0.35, those that have had 10 percent or more, match with 0.25 and 0.30

population, and follow those to two years as well.

Dr. Matoba?

DR. MATOBA: Alice Matoba. I think we still have to specify what percentage cell loss we're looking for. Otherwise you could end up with data that doesn't show significant loss, but you haven't proven that there is no -- the converse hasn't been proven. So I think we still have to specify what percent loss per year we are looking for.

DR. McCULLEY: Talking about greater than 10 percent? Or from baseline at two years? One of the problems with specular is it's not as precise as we'd like it to be.

Dr. Macsai, you were --

DR. MACSAI: Well, I was going to stick my neck out for a change.

(Laughter.)

DR. MACSAI: Dr. Grimmett's calculations, which I double-checked somewhere here, he calculated 5 percent loss per year. At 23 and three-quarters years, you're toast, or your cornea is toast. So that means if you're 25 when this is implanted, when you're 48.75, your endothelial cell count has dropped to 800 and you're on a transplant list.

DR. McCULLEY: Dr. Matoba?

DR. MATOBA: Alice Matoba. I had a question about those calculations, and that is, did you assume that it was 5 percent cell loss for the whole cornea over that period of time? But really, it was like a focal area that showed 5 percent loss, not the central or 6 o'clock. So I don't think you can assume 5 percent loss per year over all. You were probably over-estimating the effect of that finding.

DR. MACSAI: Right.

DR. McCULLEY: Dr. Van Meter?

DR. VAN METER: I would like to reiterate that point. Given the fact that this was a focal measurement and the fact that our ability to measure cells in this particular area of concern is more questionable than our ability to measure central corneal epithelial cells, I would favor just continuing to follow these patients and see where they go. It might be possible to follow all of the 0.35 cohort, but I'm not sure that -- again, I think we're collecting data and we're not sure how to manage the data we get.

DR. McCULLEY: I think that's true, that before the fact, we're not necessarily sure -- Dr. Macsai?

DR. MACSAI: Dr. Macsai. In fact, you're correct, Dr. Van Meter. This is perhaps data where we're not sure, but we're talking safety. We're talking long-

term safety of a new device. If the cohort is already enrolled, they've already been measured centrally at 6 and 10, continue to follow that cohort and see what happens.

DR. VAN METER: I thought that's what I said.

DR. McCULLEY: Okay. We had agreement before that we were going to recommend a postapproval study, and what we're trying to do is fine-tune what that specific recommendation is. What I seem to be hearing is that the recommendation is to follow for up to a maximum of two years, or for two years as a minimum for now, the 0.35 enrolled cohort. Does that accurately reflect the sentiment?

DR. ROSENTHAL: This is Dr. Rosenthal. And what about the 0.25 and the 0.30? Do you want us to sample those and continue to follow some of those?

DR. MACSAI: Yes.

DR. ROSENTHAL: I think that's a reasonable request. I think the real issue is that you don't know what's really going to happen.

DR. McCULLEY: That's right.

DR. ROSENTHAL: It's fun to follow them, but what are we going to do? I think that rather than start on another path of another prospective study, to look at these patients and look at them carefully I think is a very wise recommendation and one which I think the company could

probably live with quite happily, and would want to live with.

DR. McCULLEY: They'd probably rather not do it.

Are there any other comments about the specular?

(No response.)

DR. McCULLEY: So Question 1 is dealt with.

Question 2. "Do the assessments of visual symptoms provide reasonable assurance of safety for all three thicknesses of the ICRS?"

DR. SUGAR: That's also the same as Question 5, I think.

DR. MATOBA: No, it's not.

DR. McCULLEY: Question 2 is limited to symptoms. Question 5 brings up other issues, and that then raises a question about how best to approach this issue relative to the labeling and the different ring sizes. Dr. Grimmett had eight specific points that he brought up about the 0.35. Others, Dr. Wang and others brought up issues relative to the 0.35 and labeling. So do we want to combine 2 and 5?

DR. BULLIMORE: This is Dr. Bullimore. I think that there's a consensus that we do need to include this in the labeling, but basically it's okay and we should move on

and cover it under Question 5.

DR. McCULLEY: We can do that.

DR. MACSAI: I beg to differ.

DR. McCULLEY: Dr. Macsai?

DR. MACSAI: Excuse me. I respectfully disagree with Dr. Bullimore. I think that the visual symptoms that these patients are discussing with the sponsor represent a quality of vision, which is maybe different from visual acuity. I understand we have limitations in our ability to measure them, but it's important to include the patients who had the segments removed due to their visual symptoms, and that's not so in the table that we have. So that the statistics are lower in these tables than, in fact, if you include those patients.

DR. ROSENTHAL: This is Dr. Rosenthal. I think what you're saying is that there should be some reference in the labeling to the issue of symptoms.

DR. MACSAI: Yes.

DR. ROSENTHAL: Both for those who have maintained the ring in the cornea and for those who have had it taken out, so that patients and doctors know what they have to face when they are contemplating putting in that ring. You would like that reflected in the labeling.

DR. MACSAI: Yes.

DR. BULLIMORE: This is Dr. Bullimore. I agree with Dr. Macsai.

DR. McCULLEY: Okay. There are multiple issues. Let me do this. Let me ask Dr. Grimmett to read -- we're not going to downplay symptoms, we're not going to downplay signs or anything else. But let me ask Dr. Grimmett at this point to read his eight concerns about the 0.35 ring that would presumably be the substance of the label warning or the labeling.

DR. PULIDO: Point of order.

DR. McCULLEY: Okay.

DR. PULIDO: Are we proceeding, then, to Question 5?

DR. McCULLEY: No. We're moving 5 to 2. We're combining 2 and 5 and taking it at 2. The two are tied, so we're moving them all to one basket and we're going to deal with them now.

Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. Dr. McCulley, did you just want me to list the headers for the eight sections? Like the first was endothelium. Do you want me to just list them like that?

DR. McCULLEY: I think so.

DR. GRIMMETT: Okay. The eight issues that I believed were different for the 0.35 millimeter implant

based on the data: number 1 was endothelium; number 2 was induced cylinder greater than 1 diopter; explantation; frequency of certain visual symptoms; magnitude of certain visual symptoms; uncorrected visual acuity; stability of manifest refraction spherical equivalent; and predictability.

DR. McCULLEY: So if we recommended putting in the labeling that with the 0.35 ring there were increased concerns about those eight issues, would that deal effectively with what we want to have addressed?

DR. SUGAR: I think the specific data should be included. This is Sugar. So that there should be a table listing for each ring size, the frequency of whatever it is of those eight points that we're looking at. This would be for the physician's package.

For the patient's package, I think it would have to be put into some kind of more user-friendly wording.

DR. McCULLEY: So recommend including raw data or summary data.

DR. JURKUS: This is Jan Jurkus. The other thing I would suggest is not only including just the ring size but also the refractive data, that the 0.35 ring is for the 3 diopter myope, and if you are this moderate type of myope, these might be problems that you have,

particularly for the patients, since there are a number of other methods that can correct that patient that might have fewer symptoms. The patient might not know what a 0.35 ring size is.

DR. McCULLEY: Oh, okay. But in the labeling it would have to be clear to them what refractive error was being addressed.

DR. ROSENTHAL: This is Dr. Rosenthal. I agree that one should put in a table. I think the issue is do you emphasize the areas -- I mean, I would feel it appropriate to emphasize the eight areas that Dr. Grimmett mentioned, to present the data and then to say that these are the following problems that can exist. That's how I would proceed.

DR. McCULLEY: Both a statement and the numbers.

DR. ROSENTHAL: As well as the numbers.

DR. McCULLEY: Yes, yes. I agree.

Dr. Pulido?

DR. PULIDO: Just a question for the panel. I think we all feel very comfortable in approving -- or at least I do. I feel comfortable in approving the 0.25 millimeter and the 0.30 millimeter, but I have questions still about approving the 0.35 millimeters. We're moving along as if we are going to approve the 0.35 millimeter as

well. Do we want to first find out if people want to approve all three of them?

DR. McCULLEY: Okay. Point raised. Good point. Is there sentiment -- I mean, this gets the cart before the horse, and that's one of the problems with going down the questions. But since we're bringing up issues that are different with the three different sizes, then I guess we're working on labeling for 0.35 as though it's going to be part of the total recommendation. Is there a sentiment to continue to include 0.35 as part of our overall discussion, or should it be taken out into a separate discussion? That's trying to say politically what was already alluded to. Is there sentiment to continue discussion of all three ring sizes, with some possible differential labeling language?

DR. SUGAR: Yes.

DR. BULLIMORE: Yes.

DR. VAN METER: Yes.

DR. McCULLEY: Any dissent?

DR. MACSAI: I'd like to raise the question to our medical officer. This is Dr. Macsai. Will longer-term follow-up of the 0.35 segments that are implanted provide more data on stability, more data on the rate of explants and on the endothelium loss? Simply, do we need to look at that segment for more than 12 months? If we looked at that

segment a year from now, would we feel more comfortable approving it?

DR. ROSENTHAL: This is Dr. Rosenthal. You've already asked that it be looked at for an additional year for the endothelial, all the patients with the 0.35.

DR. MACSAI: That have endothelial cell counts. That's a subgroup.

DR. ROSENTHAL: Oh, a subgroup. I see. So now you're suggesting possibly looking at all of them?

DR. MACSAI: I'm asking the panel.

DR. McCULLEY: We're getting two questions on the floor at the same time. Let's try to get resolved the first question before we go on to whether we want additional postmarket.

Dr. Van Meter?

DR. VAN METER: I'd like to directly answer the question. I think it's reasonable to follow those patients that have already had specular -- those 0.35 millimeter implants that have already had specular started and follow them longer and see where this goes, because I don't think the additional data on additional patients -- the recruitment of more patients is not going to give us data that's helpful. I would also like to point out that the procedure is potentially reversible and the visual symptoms can be a labeling issue. But I think it's very reasonable

to include this in the discussion.

DR. McCULLEY: Okay. So is the agreement that we will continue to discuss all three ring sizes, keeping the option of differential labeling recommendations?

DR. MACSAI: Yes.

DR. McCULLEY: Is there dissent to that?

(No response.)

DR. McCULLEY: Unanimous -- oops. Karen?

DR. BANDEEN-ROCHE: This is just a question. Karen Bandeen-Roche. In terms of a bad scenario, we follow for two years and something is alarming, what happens at that point? Is approval rescinded? What happens?

DR. McCULLEY: That's an FDA policy-driven issue, I believe, and not under our purview. Not to try to skirt your issue, but it's not our issue.

Dr. Wang?

DR. WANG: Ming Wang. I just want to echo Dr. Pulido's comment just now and clarify for myself. Are we going to treat 0.35 separately or still discussing as a whole?

DR. McCULLEY: Just a moment ago we had unanimous consent that we were going to discuss all three.

DR. WANG: Okay.

DR. McCULLEY: We just decided that.

DR. WANG: As one premarket approval.

DR. McCULLEY: Yes. But we reserve the right and the ability to have labeling that is specific for individual ring sizes, if we choose.

Renee?

DR. MIDDLETON: Renee Middleton. My comment is with respect to all three ring sizes. While we're talking about the labeling under the patient booklet, when the question is asked what are the risks and we have the chart there with night vision and blurring vision, one of the things that stands out for me is the fact that it says you may have discomfort and/or pain. From a person who really dislikes pain, that stands out to me. I think that it would be helpful to indicate to the patient did everybody experience pain, how much pain, and you'd have the information. They'd report the information on pain and discomfort, 15 percent of the individuals.

Somewhere that should be reported to give me a sense that I may not have to worry about pain. But if I do, it's only like 15 percent of the individuals that they sampled.

DR. McCULLEY: Good point. So our recommendation would be, along with the -- in the labeling, to indicate the severity and frequency of pain that a patient is apt to encounter.

DR. MIDDLETON: Because two days of pain can be

significant.

DR. McCULLEY: Oh, you bet.

So is the sentiment, then, that we would have the general statement relative to the eight points that were brought up? Did we have fluctuating vision? We had 25 percent of patients with the 0.35 ring had fluctuating vision of greater than 0.5. We didn't have a stability in your eight. So there would be nine.

DR. GRIMMETT: Yes, there was.

DR. McCULLEY: Seven? Less stable. You got it. Sorry.

Does that cover all of the additional issues we had with the 0.35 ring? There was increased -- no, there wasn't.

DR. GRIMMETT: This is Dr. Grimmett. I do have some typed summary comments that I could simply hand over and you could copy them and it enumerates all this.

DR. McCULLEY: Okay. Is there agreement on the eight points, the general statement in the table with percentages? Is there disagreement?

(No response.)

DR. McCULLEY: Okay. Question 3. "Do the reports of corneal sensation losses provide reasonable assurance of safety of all three thicknesses of the ICRS? What, if any, additional data are needed to make this

decision?"

Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. I believe the answer is yes, reasonable assurance of safety. As either Dr. Schanzlin or Lemp mentioned, of the 13 that had corneal sensation losses, the 5 percent at 12 months, subsequently they all regained less than 20 millimeters of difference on the esthesiometer. Additionally, those patients with corneal sensation loss at 12 months had no evidence of corneal staining. So I think the answer is yes.

DR. McCULLEY: Would it be reasonable to put in the labeling that a decrease in corneal sensation has been noted and it's of unknown clinical significance at this point? Just to put something in the labeling.

DR. GRIMMETT: I agree. It's been noted in select patients and we have reason to believe it may be temporary in nature.

DR. McCULLEY: And of no yet-determined clinical significance.

Any other comments on that point?

(No response.)

DR. McCULLEY: Okay, Question 4. "The range for the average correction achieved with 0.25 millimeters, 0.30, and 0.35 ICRS is from -1.48 to -2.76 diopters. Does the achieved correction data support requested indications

for patient population with preoperative myopic error ranging from -1 to -3.50 with 1 diopter or less of astigmatism?"

Dr. Matoba?

DR. MATOBA: It might be less confusing to say up to -3 spherical equivalent with up to 1 diopter of astigmatism, because I think you can only implant up to -3 spherical equivalent. I think they go to -3.5 because you might have 1 diopter of astigmatism, but the way it's stated is a little vague.

DR. McCULLEY: Yes, I was confused by that. But I see sponsor shaking their head, which they're not at liberty to un-confuse us. There is the issue about the 3.50, the 3, the spherical equivalent, the sphere, and so forth.

DR. MACSAI: Spectacle plane, corneal plane.

DR. McCULLEY: Is that all it is?

DR. MACSAI: No, I think it's not.

DR. McCULLEY: What's the -3.50 at the spectacle plane or the corneal plane, or vice-versa?

DR. MACSAI: It's not the spectacle plane versus the corneal plane. My understanding from reading it is it's the spherical equivalent, because -3 plus 1 equals -3.

DR. McCULLEY: That was your understanding of

it, and that's what Dr. Matoba said, and that makes sense, but in reading the audience, which I'm not supposed to do, I'm not sure that's what was intended. We can make our recommendation.

Dr. Eydelman?

DR. EYDELMAN: I believe the indication statement is referring to spherical equivalent because the tables in my review, which came from the sponsor's submission, were in terms of spherical equivalence, preoperative CRSE cycloplegic spherical equivalent.

DR. McCULLEY: Okay. So it is a -3 upper limit spherical equivalent.

DR. BULLIMORE: No, 3.50 spherical equivalent.

DR. McCULLEY: Dr. Eydelman?

DR. EYDELMAN: Back in my slides, what I tried to break out was -- if you give me a second, I'll try to get to that slide. This is referring to greater than 3 diopters of spherical equivalent.

DR. BULLIMORE: This is Dr. Bullimore. You have a slide that's headed "Appropriate Refractive Range" and it gives the RPR for all three thicknesses and then the proposed indication. I think that clarifies it. This is the one.

DR. EYDELMAN: Does that help?

DR. BULLIMORE: Yes.

DR. McCULLEY: I think we're understanding amongst ourselves. I'm going to exercise the prerogative of asking a person from the sponsor to approach the podium, if you wish, to clarify this beyond what we have stated, which is, in effect, it would be -- the upper limit of approval would be a -3 spherical equivalent.

DR. ROSENTHAL: This is Dr. Rosenthal. Mr. Chairman, if you look at Dr. Eydelman's next slide, she has shown you the patients greater than -3 diopters spherical equivalent as well.

DR. McCULLEY: I know.

DR. ROSENTHAL: All right. So I'd like you to consider that.

DR. McCULLEY: Okay. Is it 3 or 3.50 spherical equivalence? A simple question, I think.

DR. BULLIMORE: No, that's not a simple question.

DR. McCULLEY: I knew I should never say that.

DR. BULLIMORE: If you go back a slide, the proposed indication says "for reduction or elimination of myopia of -1 to -3" blah blah blah, "in patients" quack quack quack, "with preoperative myopic error ranging from -1 to -3.50." The way I read that is that the range of likely correction is -1 to -3, but it would be labeled such that it could be done on patients up to -3.50, on the

understanding that they would be slightly, on average, undercorrected. The first clause is the correction. The second is the patient range that would be eligible.

DR. McCULLEY: And we had data that was shown on those greater than -3 that actually came in under guideline.

DR. BULLIMORE: Yes.

DR. McCULLEY: Okay. So let's just be absolutely sure that we're all on the same page.

Dr. Holladay?

DR. HOLLADAY: Jack Holladay. One comment. Could we go back to that prior slide? It's exactly what we're saying. We want to get from 1 to 3 diopters of effect in the reduction of myopia. The patients in the study went up to 3.50, and actually a little higher, that got that effect. Our question may be that we might even consider dropping that last line because there are patients, for example, that may be -4.50 or -4 who you want to be -1 and still get a 3 diopter effect.

So what we'd like to say is "for the reduction or elimination of myopia from -1 to -3," period. And the range of corrections doesn't matter.

DR. McCULLEY: That becomes a practice of medicine issue. So your request, then, is -1 to -3 spherical equivalent.

DR. HOLLADAY: Correction.

DR. McCULLEY: Correction, and dropping the second portion of this.

Dr. Eydelman?

DR. EYDELMAN: If we follow that suit, we have to somehow assure ourselves that, since we don't have any data, that if we implant the 0.35 millimeter ring in a 5 diopter myope, we're still going to get 3 diopter correction. I don't know that.

DR. MACSAI: We have no clue about that. That data hasn't been presented, and as you said earlier, Jim, I believe that's a practice of medicine issue regarding monovision, et cetera, or presbyopia. But really upon explanation, reduction of -1 to -3 diopters of myopia -- do you understand?

DR. McCULLEY: Yes. It is in this patient population. The second part is qualified.

DR. MACSAI: You need to have it, because otherwise you could have -4 plus 2.

DR. McCULLEY: Good point. Then the question comes back, are we comfortable with it being -3.50?

DR. MACSAI: Yes.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Yes. From Table 4 of page 40 of Dr. Eydelman's review, 99.8 percent were less than 4

diopters, and 99.1 percent were from 0.5 up to 3.5 diopters. So I think by putting it as presently labeled would be very reasonable.

DR. McCULLEY: General sentiment to that, now that we're unconfused and all understand what we're talking about? Is there any disagreement?

(No response.)

DR. McCULLEY: Are you satisfied, Dr. Eydelman?

DR. EYDELMAN: Yes.

DR. BULLIMORE: This is Dr. Bullimore. I'm in violent agreement with myself.

(Laughter.)

DR. BULLIMORE: The only issue I want to raise, and I raise it tentatively, is the issue of overcorrection. Given the fact that we've set the lower limit of the range at -1, and the average effect for the 0.25 millimeter device was about 1.5, if a patient comes in as a -1 and gets the 0.25, their most likely expectation is that they're going to be overcorrected by half a diopter. Of course, there's quite a reasonable chance that they will be overcorrected by quite a bit more. Do we want to include something in the labeling about the possibility of overcorrection in low levels of myopia? I just offer that. If it dies, I'll die with it.

DR. McCULLEY: Other comments?

DR. SUGAR: I think that's very reasonable.

DR. McCULLEY: Okay. Any other discussion one way or the other?

(No response.)

DR. McCULLEY: So basically what you're saying is that there should be a warning in the labeling that a -1 or thereabouts with the 0.25 ring has a risk of being 0.5 diopters or more overcorrected.

DR. BULLIMORE: Yes.

DR. McCULLEY: That would be in the labeling. Is there agreement?

DR. SUGAR: Yes.

DR. McCULLEY: Disagreement? Dr. Macsai.

DR. MACSAI: Do we have data to suggest that "or more"?

DR. BULLIMORE: The main change with the 0.25 ring, which presumably would be the one you'd put in a -1 myope, was 1.5 diopters. So the average change is going to take the patient to +0.50. So there's a 50 percent chance they're going to be that side of the line, and a 50 percent chance they'll be on the other side.

DR. SUGAR: The standard deviation is 0.52.

DR. MACSAI: Okay. Thank you.

DR. McCULLEY: Other discussion on that point? Karen.

DR. BANDEEN-ROCHE: Dr. Bandeen-Roche. It might make it clearer just to state that the mean correction was -1.48. Therefore, there is some reasonable chance of overcorrection in people with myopia much less than that.

DR. McCULLEY: Okay. Any further comments?

DR. BULLIMORE: I live.

DR. McCULLEY: Despite your violent agreement with yourself? If you don't get into a violent disagreement with yourself. Actually, you used to have a full head of hair, right?

(Laughter.)

DR. McCULLEY: Okay. We've done 5. Wait. We're not through with 4? Oh, 5. Yes, you're right.

"Do the safety and effectiveness outcomes support approval of 0.25, 0.30, and 0.35 ICRS? Is distinct labeling warranted for any one of the three proposed ring thicknesses?"

We covered much of that before, but there are some things we didn't.

Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. Since we lumped 2 and 5 together, I held my comment on 2 until we got to 5 here.

(Laughter.)

DR. GRIMMETT: I want to reiterate what I already commented on, but just to reemphasize it. It's my belief that both in the patient booklet and in the physician information, if it's not already done, which it may be, that the frequency and magnitude data reflect often and always categories combined, as well as moderate and severe categories combined. I think it downplays visual symptoms to only report the severe and always categories. I think that's very important.

DR. McCULLEY: My interpretation of the data was that there was significant increase in symptoms that were of increasing magnitude going from 0.25 to 0.35, but they were real at 0.25.

DR. MACSAI: Absolutely.

DR. GRIMMETT: Because if you combine those figures, up to approximately 1 in 5 can have visual symptoms that certainly reflect a new set of higher order visual aberrations occurring in those patients. I believe that's important to know.

DR. MACSAI: Higher, 37 percent.

DR. ROSENTHAL: I don't think it's fair to combine them. I think it's fair to put them both in, but I'm not sure it's fair to combine them, just like you wouldn't combine zero and 1 to make a half. You put in moderate and severe. You don't leave them out. But to say

moderate or severe, I think it's fairer to give the patient and the doctor some idea of these very difficult terms. What is moderate and what is severe for Dr. Macsai may not be moderate and severe for me. But at least it's better than combining moderate and severe.

DR. McCULLEY: So it just means more data.

DR. GRIMMETT: I completely agree. More information is better than just listing the two columns, so people can have a balanced appraisal of what's going on.

DR. McCULLEY: Karen?

DR. BANDEEN-ROCHE: Dr. Bandeen-Roche. This is a global issue not connected to one of the three sizes. It might be redundant. It's the issue of those patients who I would say fail altogether, to make sure that there is some labeling that is very clear about that, which means patients whose surgeries had to be aborted, just didn't succeed in the first place, and patients who end up explanting ultimately being reported as a percentage for which that happens and not being mixed up about do visual symptoms include these people or not. We just have to be very clear, and I'd like to see an up front statement of this may not work for you at all, the percentages, thus and such, being clear about what that means.

DR. McCULLEY: So we need a strong statement in labeling about the 4.7 percent incidence of explantation,

and that those patients represent additional problems above and beyond those reported in the symptom percentages.

DR. BANDEEN-ROCHE: Right, and a very small percentage for whom the surgery never succeeded in the first place, 5 out of 454, something like that.

DR. McCULLEY: I don't remember the exact number, but okay.

Dr. Wang?

DR. WANG: Ming Wang. The question is, is distinct labeling needed just for the 0.35 or not, or is it sufficient just providing that table including all three? My feeling is that 0.35 is somewhat different animal, and we may need to put a sentence for the patient's sake, rather than just present a table neutrally, all three sizes, but have one sentence or two warning about this, because it is doubling in the visual symptoms of 0.35 compared with the other two. It's non-linear.

DR. McCULLEY: The sentiment has been there, and that was well stated, that the additional problems with 0.35 should not be just buried in the table for a person to sort out and realize that there is significant increase at the 0.35 ring.

DR. SUGAR: That was the Grimmett proposal.

DR. McCULLEY: Right, Grimmett-Wang.

Dr. Macsai?

DR. MACSAI: I would also like to suggest that, as far as the effectiveness outcomes, that not only the plus or minus 1 diopter of intended correction be included, but also the plus or minus 0.5 diopter, because we're talking about such a low range of myopia in these patients. If you're -1, plus or minus 1 doesn't mean much.

DR. McCULLEY: You're talking about in the predictability and stability label warning?

DR. MACSAI: Not warning. Labeling.

DR. McCULLEY: Okay, labeling.

DR. GRIMMETT: This is Dr. Grimmett. That may already be done in the labeling that they presented, both the data for plus or minus 0.5 and plus or minus 1.

DR. MACSAI: Right.

DR. McCULLEY: But I think the point is, rather than a naive patient who is a -1 not taking that into account, that there needs to be added wording for that person to be sufficiently aware.

Any other comments on Question 5?

(No response.)

DR. McCULLEY: Question 6. "Is the current data in the Removal Cohort sufficient to support reversibility claim? If not, what is the minimum number of eyes and the minimum length of follow-up that you recommend for this assessment?"

Dr. Van Meter, do you want to start that?

DR. VAN METER: Woodford Van Meter. I think the data support the reversibility claim. I don't think that the adjustability claim can be supported, but I think the reversibility claim is adequately supported by the data.

DR. McCULLEY: Okay, we're just talking about reversibility now. We'll come to adjustability the next point. Reversibility is on the table.

Karen?

DR. BANDEEN-ROCHE: Karen Bandeen-Roche. Whether reversibility is supported depends on what we consider to be adequate reversibility. I computed some rough lower confidence bounds based on the sample of 21, and then assuming the same percentages in 34. Just to very briefly summarize, there is very weak evidence, even at 21 over 21, that reversibility for BSCVA is higher than 94 percent, very strong evidence that it's higher than 70 percent, and then a whole range in-between. So, yes, it really depends on what we think is an acceptable percentage re-achieving their preop status.

DR. McCULLEY: Right. I'm not sure about that. Is there some way that you could phrase this to take the reality as presented under consideration, rather than an all or nothing?

DR. BANDEEN-ROCHE: Well, the 95 percent confidence bounds that I -- these are exact lower confidence bounds that I roughly computed, back of the envelope sort of a calculation, were 0.87 for best corrected visual acuity, 0.79 for post-removal predictability, 0.73 for manifest refraction cylinder. Again, that was at 21. I realize there's been some additional data since then, but if you extrapolated that out to 34, those quantities would be 0.91, 0.82, and 0.75, respectively.

DR. McCULLEY: Could you put a recommendation into words that would be appropriate for labeling?

DR. BANDEEN-ROCHE: I think that it's beyond my purview to suggest clinically what is an acceptable target for reversibility. So I think that has to precede a recommendation on my part.

DR. MACSAI: Dr. McCulley?

DR. McCULLEY: Dr. Macsai.

DR. MACSAI: I just want to raise the question that there appears to be reversibility of visual symptoms and vision, but I didn't see any data about reversibility of changes in sensation, endothelial cells, contrast sensitivity in those patients.

DR. McCULLEY: Dr. Grimmett brought that up in his review. The symptoms were not completely reversible,

nor was the refractive error completely reversible. But, then again, the point that Karen is bringing up is what is acceptable? What kind of guideline would we have for acceptability stating that we agree it's reversible? It is reversible to a degree. Is it reversible to a sufficient degree that that statement should not be qualified in some way?

Dr. Van Meter, then Dr. Sugar.

DR. VAN METER: The recent data that was submitted at the end of December with the final packet -- and perhaps we can do this just by reiterating some statements from that final report. No subject lost best corrected acuity. Ninety-six percent of patients returned to plus or minus 1 diopter of their manifest refraction. The one that was outside that particular bracket was better. Stability appears to have been shown at three months, and all of the patients that had cylinder appeared to return when the implants were taken out. I think you might say that the loss of glare symptoms or endothelial cell counts, we really don't have any data on that, and I think you can say that is not known. But I believe we have reasonably good data.

DR. McCULLEY: I thought we had the data on symptoms but we didn't on endothelium or corneal sensation, slit lamp appearance and so forth.

DR. SUGAR: This is Sugar. For the symptoms, there were two patients. All patients had zero to 1 for all of the subjective symptoms, except for two patients, who had three symptoms -- severe difficulty with night driving, double images, and fluctuating vision. I think that it's appropriate to have a statement that it is reversible and list the parameters under which it is so for all patients 20/20 or better best spectacle-corrected visual acuity. Two of 21, or whatever the denominator becomes, had symptoms that were moderate or severe. These are two patients with those three symptoms.

DR. McCULLEY: So just put data in the labeling.

DR. SUGAR: And just put the specifics there.

DR. McCULLEY: Karen?

DR. BANDEEN-ROCHE: As long as it's very clear the amount of data that contributed to this, I think I'd like to make it even stronger to get people to stop and think about what strength of evidence that means. Now, maybe for the physician's booklet a lower confidence bound would do it. I still think it's worth at some point FDA and all of us thinking about what is acceptable. But in the meantime, there needs to be some measure whether 21 out of -- well, I'm sorry, it's now 28 out of 28, whether that's very powerful evidence or very weak evidence, or

something in between. I would suggest put the confidence bounds in there for the physicians.

DR. ROSENTHAL: This is Dr. Rosenthal. You know, it becomes a philosophical issue what is reversible. If patients have unrealistic expectations that this can be put in and just removed with complete assurance that there will be no problems, that would be -- I would consider that a reversible situation. But I don't think that's absolutely the case. Hence, one could, instead of using the word -- I'm just throwing this up for panel's consideration -- instead of using the word "reversible," use some other word saying that it can be removed, and therefore there's a 96 percent chance that you will get back to normal, but there's a chance that there's going to be some serious problems. That's a realistic evaluation, rather than calling something reversible.

DR. McCULLEY: I think that makes sense.

Renee?

DR. MIDDLETON: As a consumer, if you told me that something was reversible, I would assume that you meant that I would go back to where I was, your former statement. That would be my assumption. So if that's not the picture that you want to leave with the consumer, then perhaps some other wording is appropriate, or more language to clarify what you mean by reversibility.

DR. McCULLEY: Or a 96 percent probability of reversibility. Something.

DR. MACSAI: Removable.

DR. McCULLEY: Well, it is removable, but it's largely reversible. We need a better word because, as indicated, in our human mind, when we hear reversible, we assume return to baseline. It has a probability but not an absolute certainty of doing that. How do we want to have that -- how can that be honestly, effectively conveyed?

Marcia?

DR. YAROSS: This is Marcia Yaross. What I would suggest, instead of struggling over the semantics, is just have a factual description of what were the results observed and basically state that in a group of X patients who had this device removed, X percent recovered their vision to the previous levels. I'd also point out as a benchmark in terms of effectiveness numbers in the ranges of 84 to 88 percent achieving an effect have been considered effective by this panel in the past. So 100 percent is not necessary to determine that something is effective.

DR. McCULLEY: As long as it's done so that reversibility is not what stands out and there's a footnote that might be ignored. So if we take the word out, you're suggesting to --

DR. YAROSS: I'm suggesting a factual description of what happened to those subjects that had the device removed.

DR. ROSENTHAL: This is Dr. Rosenthal. There's no question that that's what would be done. The question is that the company is going to want to say it is reversible. That is a very powerful claim that they will want to make in their marketing of the product, as compared to the other modalities of refractive surgical intervention. So I think it's a very important issue what we allow them to say and what we allow them not to say. Certainly in the labeling we would spell it all out, but are you going to let them say it's reversible?

DR. YAROSS: Marcia Yaross again. That's why I was trying to propose that something in the 80 percent is what's been our criterion. So if we agree on what reversibility should mean, then you don't need to be 100 percent to say you're effective in some regard, based on the history of this panel.

DR. McCULLEY: Just one point here. We're getting into the world of lay people and their definitions of words, not the scientific community, with an arbitrary softening of a definition. I think Renee's point is very well taken, and I think that the population, if they hear reversible, they're going to assume it is absolutely

reversible. This is not only caveat emptor but caveat venditor. It's who's buying and who's selling. So informed consent and the risk of someone selling something that is reversible that ends up not being truly reversible, the patient is going to be unhappy because they use the word reversible as they would use it in their normal daily lives.

Eve, I think you had something to say.

DR. HIGGINBOTHAM: I was going to offer "somewhat reversible."

(Laughter.)

DR. HIGGINBOTHAM: The suggestion is that this is only up to three months of data, and I just question whether or not that's long enough. I know in glaucoma we like to see at least six months. Because the refractive stability seems to get better up to 12 months, I don't know if three months is really enough.

DR. McCULLEY: Again, we need a thesaurus to come up with a better word.

Renee?

DR. MIDDLETON: I think we can see that there is a difference between misleading and outright lying, but they're not doing either. I think if they simply said -- I would be comfortable if you said reversibility. I don't have a problem with that as a consumer, as long as you tell

me in what framework you're referring to reversibility as, and that's up front to the patient. Then I wouldn't feel like they were misleading me. With the data that's there, I don't think they're intending to mislead, unless you just said reversibility and leave all that information out.

DR. McCULLEY: Okay. Dr. Pulido?

DR. PULIDO: Dr. Middleton, I agree on a lot of things with you, but on this one I disagree because people are going to fixate on that word and forget the rest. I think we still should struggle with this and make it a more equitable term than reversible.

DR. McCULLEY: Dr. Wang?

DR. WANG: Ming Wang. I would like to suggest maybe language something like this: "This device can be removed and the majority of symptoms are reversible," and provide a table, or "is largely reversible." Some language, immediately followed with a table.

DR. McCULLEY: Dr. Eydelman?

DR. EYDELMAN: If the panel chooses to come up with different language, we're still going to need the recommendation from the panel as to what would constitute a reversible claim that the sponsor can then come back with enough data, because that claim I have a feeling will come back. So even if we choose not to call it reversible at present, can the panel then make a recommendation as to how

much data would be needed for the sponsor to be able to make that claim?

DR. McCULLEY: Reversible as has been suggested is an all or nothing in the mind of the public, and it's going to have to be clarified if it's anything less than absolutely reversible. Just on that point, is there agreement to that point, to use the word reversible as it is used? We can't make this a scientific term that we put under a guideline. It's used in common, everyday language, and I think we understand how it's understood.

Dr. Sugar?

DR. SUGAR: I think this affects how the company markets their product, and I think people market refractive surgery as in most circumstances you will no longer need glasses for distance vision, and I think it's reasonable to say that this is reversible in most circumstances, because I believe that it is.

DR. McCULLEY: Okay, as long as it's qualified, and then how much qualification, how specific should the qualification be. It just has to be qualified and not lost as a footnote.

Karen?

DR. BANDEEN-ROCHE: Dr. Bandeen-Roche. Might you also want to put a comment in there for the lay person that, however, only thus and such many patients have been

evaluated for only three months of follow-up and more data will solidify -- something like that, you know?

DR. McCULLEY: That makes sense as well.

Dr. Matoba?

DR. MATOBA: Alice Matoba. I agree with Dr. Sugar regarding his comments about the reversibility. Also, I wanted to suggest that maybe we consider adding a statement that the average residence of the implants was about 10 months and that we don't have information regarding potential reversibility following long-term residence in the cornea.

DR. McCULLEY: Good point.

Dr. Pulido?

DR. PULIDO: What about the endothelial cell loss? That is not reversible.

DR. McCULLEY: We don't know. We don't know whether it's significant or not yet, so we really can't address that. We don't know that it's there yet.

Dr. Macsai?

DR. MACSAI: It seems to me that you and Dr. Pulido and Dr. Higginbotham and Dr. Sugar have just answered this question. We do not know if the endothelial cell change is reversible.

DR. McCULLEY: Well, we don't know if it's real yet.

DR. MACSAI: Well, that's right. So we don't know, and we only have three-month data. I think "removable" is a great word. There's no eraser at the end of a laser, but this is removable. Take it out. I mean, that's a big selling point.

DR. McCULLEY: Not nearly as big a selling point as reversible.

(Laughter.)

DR. MACSAI: But we don't know.

DR. ROSENTHAL: This is Dr. Rosenthal. The company is not going to put "this is largely reversible," or "under circumstances mostly reversible." The company is going to want to say it's reversible. I must say, I have a little problem with it, because I do genuinely feel that it means it's reversible, you can erase it completely and go back to where you were, and I'm not sure that's totally true.

DR. McCULLEY: Well, we know it's not totally true, and the panel is in agreement with you.

DR. MACSAI: We don't know, so we should not say.

DR. YAROSS: Mr. Chairman, can I offer a possible clarification? This is Marcia Yaross. Or an alternative? And that might be to say that the refractive effect is reversible. It has a reversible refractive

effect, and that leaves open the fact that some of these other safety issues, it is not yet known.

DR. McCULLEY: To me, that obfuscates and it implies other things, so I don't think that's a good solution to it. I'd like to hear one. It's out there.

Renee?

DR. MIDDLETON: I think I liked what Dr. Sugar proposed, but I hear Dr. Rosenthal saying that the sponsors are not going to accept that.

DR. ROSENTHAL: This is Rosenthal. I didn't say they weren't going to accept it. What I said was, as you know, if you're a sponsor and you've got a product, you want to try to sell it using the best buzz words you can use. That's my only point. I don't want the company to be in any doubt about what the panel feels they should be allowed to say. That's what my point is.

DR. MIDDLETON: Can I ask Dr. Sugar to repeat the language that he would recommend? I believe it was him.

DR. SUGAR: I don't think that Dr. Rosenthal is going to leave the sponsor in any doubt.

(Laughter.)

DR. MIDDLETON: But what was the language that you proposed?

DR. SUGAR: Reversible in most circumstances.

DR. MIDDLETON: Reversible in most circumstances. I would be comfortable with that as a consumer. But if you have -- I'm speaking from the role of a consumer. If you have serious concerns about that language and the sponsors would refuse to use that language, I would say that they can't then say it's reversible if they're going to be uncomfortable with proposed language similar to that.

DR. McCULLEY: How about "reversible in most but not all circumstances"?

DR. MIDDLETON: That's similar.

DR. ROSENTHAL: I get the gist, and I think the big issue will be with our compliance section if there are issues relating to complaints about ultimate claims.

DR. McCULLEY: Dr. Eydelman?

DR. ROSENTHAL: But I understand, and I think the company understands as well.

DR. EYDELMAN: I know we're all trying to discuss the best term, but if we can just step back, I wanted to make sure that I'm clear on the panel's feeling about the appropriateness of stability between -- only two measures were taken, one and three months. This is different than all other stabilities. It's different than our guidance, et cetera. So before we conclude with the best term, I wanted to make sure I understand what the

feeling is about that.

DR. McCULLEY: Good point. I mean, we're cutting a corner on our guidelines. The definition of stability is within a diopter three months apart.

DR. EYDELMAN: At least two measurements at three months.

DR. MACSAI: We need six-month data.

DR. EYDELMAN: Granted that's not the same device, but --

DR. SUGAR: Preoperatively at three months post-removal, 100 percent of patients were within -- or 96 percent of patients were within plus or minus 1 diopter. That meets the guideline. And the one patient who wasn't was actually less myopic than they started.

DR. EYDELMAN: No, but you had a big dip in the curve. That definition came into assuming some kind of a linear curve. So you need to look at the points post-removal.

DR. McCULLEY: Post-removal. One month and three month were the time points that were measured.

Dr. Bullimore?

DR. BULLIMORE: I think there's a danger here that the sponsor is put in an untenable position, and I want to speak out on their behalf. They produced a device that seems to be reasonably safe, reasonably effective, and

in 5 percent of people it needs to be explanted. We're arguing over those 5 percent as to whether it should be reversible. What do we want them to do? Do we want them to produce something that fails in 10 percent so we have more data to go on?

(Laughter.)

DR. BULLIMORE: We're trying to make the best of the data that we have, and to sort of say we need to go out further and argue about the stability I think is really disingenuous on the part of this panel, and I think we should just put closure on this item and move on.

DR. McCULLEY: I think it's very important with what we do to be certain that patients are adequately informed. If we tell a patient that they are getting a procedure done to them that is reversible, then we do them a disservice if it is not 100 percent reversible. That's not to say it's not an acceptable or good procedure. It's that the patient needs to be effectively informed of what they can expect. So I don't think that's being disingenuous.

DR. BULLIMORE: No, but I think we're getting outside of what is reasonably expected of this panel and what is reasonably expected on the part of the agency of this panel. The agency has compliance people. This seems to be in their court. Whether this group of people can

agree on what's reversible and what's not seems to be a moot point. The advertising, the promotion of these devices, we're basing it on a small number of people. We have the data here. Let the FDA do what they want with it.

DR. McCULLEY: I think the FDA is asking us for our opinion.

DR. BULLIMORE: I think they've heard enough opinion. We can sit here until 7:00 discussing this and not get any closer.

DR. McCULLEY: I think we'll get closer. We're not done yet.

Alice?

DR. MATOBA: Alice Matoba. I wanted to say that I don't think anything in medicine is 100 percent. If you're going to hold people to 100 percent reversibility as a standard, no one will be able to achieve that. I think they've come close enough to showing reversibility that they can use that word in some way.

DR. McCULLEY: I don't have a problem with that. It just has to be qualified, and it has to be qualified so the lay person will understand the qualification and not skirt over it. I think Joel's reversible in -- what was it?

DR. SUGAR: In most circumstances.

DR. McCULLEY: In most but not all, and then

that underlines that it's not all for the human mind, not to skip over and not pay attention. I would be comfortable with that statement.

Dr. Grimmett?

DR. GRIMMETT: We said this before, but I'll throw it in because it has to do with reversibility. Regarding claims that patients may elect to have an alternative refractive surgical procedure performed, there's no data at this point to support that claim. That was an Amendment A attachment to page 25. So I think those claims need to be removed.

DR. McCULLEY: Right. Okay. Another point that I would agree with as well. We don't have data to make this statement one way or the other.

Dr. Sugar?

DR. SUGAR: Just to get back to Malvina's point, in Volume 8, Section I, page 11, they have from day 14 to month 1, 94 percent changed less than 1 diopter, and from 1 month to 3, 24 out of 24 changed less than 1 diopter. So I think that there is evidence that there's a plateau.

DR. EYDELMAN: Right, but from day 14, I believe there was something about 14 eyes.

DR. SUGAR: Eighteen eyes.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: I just would like to ask if maybe you, Mr. Chairman, would want to ask the panel if we feel comfortable with Dr. Sugar's recommendation so we can move on.

DR. McCULLEY: Okay. Dr. Sugar, would you restate your recommendation? And we'll take a panel poll.

DR. SUGAR: Sure. This procedure in the labeling could be stated as reversible in most but not all circumstances.

DR. McCULLEY: Is there comfort with that statement?

DR. PULIDO: How about removable and reversible in most circumstances?

DR. SUGAR: It's always removable.

DR. MACSAI: Out to 10 months.

DR. McCULLEY: We have to have the qualification that this is based on data that is on a small number of patients with short-term follow-up. So it has to be qualified. We go along with the statement as though it appears that it's okay, but we don't have long enough data or enough patients yet.

MS. LOCHNER: Excuse me, Dr. McCulley. There was one question that was raised earlier that I really haven't heard the panel discuss, and it speaks to this question of reversibility. I think it was Dr. Bandeen-

Roche who said that the number of eyes that were evaluated, whether it's the 21 or the 34, gives you a lower confidence interval on this reversibility claim that is at some points, I think you said, as low as 70 percent. I guess I would like to hear what the panel -- that's sort of setting a threshold of an absolute amount of equivalence to support a claim such as this, and I hadn't really heard whether that was felt to be adequate, the fact that the sample size you have only gives you assurance down to about 70 percent.

Now, I don't suggest that the sponsor have more failures, but there certainly could be more eyes enrolled and the sample size itself increased so that you have better confidence in the data. And I'm sure I didn't get the absolute percentages correct.

DR. BANDEEN-ROCHE: This is Karen Bandeen-Roche. I just wanted to clarify that wasn't for all outcomes. That was for, I think, manifest stability at plus or minus 0.5. It was whatever one had the lowest achieved percentage.

DR. BULLIMORE: This is Dr. Bullimore. Just a point of clarification. What is the 0.71? Is that a proportion?

DR. BANDEEN-ROCHE: It's a lower confidence bound on the proportion reversible.

DR. BULLIMORE: Okay. So the sample or the --

DR. BANDEEN-ROCHE: The actual proportion in that case was 0.88.

DR. BULLIMORE: And the lower 95 percent --

DR. BANDEEN-ROCHE: The 95 percent confidence bound is 0.75, given --

DR. BULLIMORE: So it's a proportion.

DR. BANDEEN-ROCHE: That's the unit.

DR. BULLIMORE: That's the unit. That's what I want to know. Okay.

DR. PULIDO: And therefore it's still reversible in most cases.

Can we move on?

DR. McCULLEY: I don't think we want to set any mark at a 70 percent confidence that would come back to haunt us.

MS. LOCHNER: No, I just think hearing your opinion on that was all we really wanted.

DR. McCULLEY: We're trying to hedge, and I think we're trying to accept that sponsor wants the word somewhere in there reversible, and it seems to be a reasonable request, but it has to be qualified.

DR. BANDEEN-ROCHE: If I may, Karen Bandeen-Roche. I just want to make sure I'm being absolutely clear because Dr. Grimmett thinks that I have not been.

(Laughter.)

DR. BANDEEN-ROCHE: I thank you for this.

We're talking about a 95 percent confidence bound. The value of that bound is 0.75.

DR. McCULLEY: I knew I didn't understand.

Any other comments on that?

(No response.)

DR. McCULLEY: Thank you very much. So are we okay on this point? Is the FDA okay on this point? Are we tired of this point?

Question 7. "Is the current data on exchange procedures sufficient to support claim for adjustability of refractive effect? If not, what is the minimum number of eyes and the minimum length of follow-up that you recommend for this assessment?"

Let's take this question in two parts. I think there was fairly uniform agreement among the primary reviewers. Is the current data on exchange procedures sufficient to support the claim of adjustability?

DR. SUGAR: No.

DR. BULLIMORE: No.

DR. MACSAI: No.

DR. McCULLEY: Does anyone have any countering argument to that stated opinion?

(No response.)

DR. McCULLEY: Okay, now to the more difficult

part. If not, which we're not, what is the minimum number of eyes -- and the record should show that that was a unanimous no -- what is the minimum number of eyes and the minimum length of follow-up that you'd recommend for this assessment?

Dr. Sugar.

DR. SUGAR: I don't think we can come up with a number because the predictability was so low in the few patients that they did that we don't have any idea of what the efficacy is going to be. We don't know where to grab a number.

DR. McCULLEY: We respectfully wish not to get put in that corner.

Any other comments?

(No response.)

DR. McCULLEY: Question 8. "The sponsor would like to make a claim of 'enhanced visual performance' in their labeling. Do you feel that the data in this PMA support this claim?"

DR. SUGAR: No.

DR. MACSAI: No.

DR. McCULLEY: The sentiment being stated is no. Is there dissent to that sentiment?

(No response.)

DR. McCULLEY: Unanimous no, that it does not

support the claim.

Does the FDA need further comment from panel? There's been a lot of comment that has all been in one direction. I realize just as you may have fights in the future relative to reversibility, which is going to be a major marketing issue, that you may have future fights about this issue. Do you have sufficient information relative to why the panel feels the way it does, or do you need more?

DR. EYDELMAN: I believe we have enough.

DR. ROSENTHAL: This is Dr. Rosenthal. May I add that if there really is a conflict between the sponsor and the agency, the sponsor can make a proposal to do a study to which the claim that they wish to promote will be acceptable and the study can be done. So there's no impasse as long as the company cooperates.

DR. McCULLEY: Those of you who looked at the physician training, we didn't ask the sponsor about what they were putting as a recommended upper limit for the suction ring being applied with a pressure in the range of 80. In the physician instruction portion, was a limit stated and recommended? Because I can imagine if a person is not adequately warned and not watching the clock, that an eye could be highly -- five minutes?

DR. MACSAI: Five minutes?

DR. McCULLEY: Five minutes?

Dr. Higginbotham, would you like to comment?

DR. MACSAI: What's that based on?

DR. HIGGINBOTHAM: This is Dr. Higginbotham. Five minutes at 80 millimeters of mercury is certainly a long time for any eye, particularly when you've only assessed these eyes by super threshold testing. So I would have some particular concerns about that duration. Certainly the literature suggests four minutes is the absolute maximum, but something less than that even would be more acceptable. So if the ideal time and what your experience has dictated in the procedures you've done to date mostly being a minute and a half, I would limit it to a minute and a half as a goal.

DR. McCULLEY: Based on experience with LASIK, I think one can go past a minute and a half before panicking. But, boy, I would never go to five minutes. I think this is going to be important for labeling and instruction of physicians, that they know the clock has to run. I'm not even sure that docs doing some of these other procedures that pressure eyes are effectively watching, but we haven't had the opportunity to make the comments to them.

What would you consider -- a minute and a half is too short.

DR. HIGGINBOTHAM: Well, I guess I'll yield to those clinicians that are currently doing LASIK in the same population. So I would yield to your wisdom, Dr. McCulley.

DR. McCULLEY: Well, it's seat-of-the-pants rather than wisdom. But I start to worry big time at two and a half, and I wouldn't go past three. But that's not based on any good, solid data, unless the person from whom I adopted that, and I couldn't tell you who it was, had good, solid data.

Dr. Wang?

DR. WANG: Ming Wang. Accompanying all LASIK surgery practice, a two-minute threshold was based on case reporting in one of the international conferences, LASIK beyond two minutes. Two minutes is the common upper limit in LASIK.

DR. McCULLEY: So you use two minutes.

DR. WANG: Yes.

DR. McCULLEY: Based on one case?

DR. WANG: Yes, based on one case, I believe in South America.

DR. McCULLEY: Okay.

DR. HIGGINBOTHAM: I missed that case report. Sorry.

DR. McCULLEY: Does anyone else have any comments about this? I think we would be uncomfortable

with five minutes. I think that this is going to be extremely important for the company to pass on to the surgeon.

Dr. Macsai?

DR. MACSAI: This is a technical question. You put the suction on and cut clockwise and counter-clockwise. If you extend beyond one and a half or two minutes, can't you take it off, put it back on, then do the other half? Why not?

DR. HIGGINBOTHAM: Dr. Higginbotham. I guess my comment interpreted the five minutes as being continuous application of vacuum for five minutes. But certainly if you allow the nerve to perfuse intermittently, as we do when we're massaging eyes post-retrobulbar, I think that would be sufficient. But again, we're going on more anecdotal information at this point.

DR. McCULLEY: But it would be better to have one and a half minutes with a break, and then one and a half minutes again, rather than three.

DR. HIGGINBOTHAM: Agreed.

DR. McCULLEY: So I think direction to FDA to pay very close attention to working out something with the company for guidelines relative to the length of time for continuous suction, and if that is exceeded, how long the eye should be allowed to perfuse prior to reestablishing

suction.

Dr. Pulido?

DR. PULIDO: Can I ask a separate question at this time?

DR. McCULLEY: Yes.

DR. PULIDO: I'm still very concerned about the marked difference in results between different sites, and I would like to see something in labeling, a statement in the labeling to the effect that there can be marked variability in results in explantation rates between different surgeons.

DR. McCULLEY: Boy, I'll tell you, that opens up, I think, from some different vantage points that we won't talk about in public forums, some real potential cans of worms.

Dr. Higginbotham?

DR. HIGGINBOTHAM: I would have some concerns about putting that in, just because the dialogue that occurs between a patient and physician and the decision that follows to take a device out can be independent of the technical outcome of that procedure but maybe some other subjective reasons that are more patient based. So I would not tie the sponsor's hands with that kind of statement.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I have another suggestion to

make.

DR. McCULLEY: Along these lines? Let's be sure this point is resolved. Is it still on this point?

DR. BULLIMORE: No, it's not on this point.

DR. McCULLEY: Okay. Any other comment on this point? Dr. Macsai?

DR. MACSAI: I agree with Dr. Pulido's observation. However, it seems to me inherent in any surgical procedure that there's going to be variability between surgeon to surgeon, whether it's an intracorneal ring, an intraocular lens, or a laser. There is going to be variability, and I would ask that the agency determine if this was a -- I assume from their bio, as we just learned about, that this was not an issue.

DR. McCULLEY: Other comments on this issue? Dr. Bullimore?

DR. BULLIMORE: It's not on this issue.

DR. McCULLEY: No, no. We're going to a new issue now.

DR. BULLIMORE: Oh, I get a new issue. Oh, goody.

In the proposed indication, the sponsor says that refractive stability preoperatively is defined as a manifest refraction change of 1 diopter or less for at least six months prior to the preoperative examination.

That seems a very generous definition of stability compared to what currently resides in the guidance document, and I would propose that we adopt something more consistent with other such standards.

DR. McCULLEY: Dr. Rosenthal?

DR. ROSENTHAL: Unfortunately, the definition of preoperative stability has varied, and this sponsor worked on the definition which was presented to you, and I think the study was done with that definition and it would have to be carried through.

DR. McCULLEY: I understand what you're saying, and I understand what Dr. Bullimore is saying, and I had the same concern.

DR. ROSENTHAL: I know.

DR. McCULLEY: It's back to the point of we have now fine-tuned, we have moved forward, we now have something we think is better, so now do we carry forward something that wasn't? Yet that's how they did the study. There must be some way to deal with both points effectively. For instance, it could be stated that, in effect, that's how the study was done that led to approval. However, current FDA guidelines are 0.5 millimeter change no greater than in the past year. So we bring into this previous, now not-so-good decision where we are now.

DR. BULLIMORE: The sponsor can collect data

on, say, -1 to -20 diopters, and this panel might vote for approval on -1 to -2. So just because a study has been done under a different set of entry criteria which is distinct from proposed indications for the public release of the device, I would argue that we should adopt a more conservative definition of preoperative stability.

DR. McCULLEY: I think in current practice a diopter variation or close to it in a six-month period would not represent a patient that was an appropriate person for keratorefractive surgery. That's not adequate stability in the real world now. This doesn't disadvantage sponsor, can put both pieces of information in, hopefully.

Dr. Eydelman?

DR. EYDELMAN: I just had a response to Dr. Bullimore's comment. When sponsor does a study on a large refractive range and then we choose to limit it, it's usually based on data. Unfortunately, we don't have any data on a tighter preop stability.

DR. McCULLEY: So can we use my argument rather than his?

DR. BULLIMORE: Oh, please.

(Laughter.)

DR. EYDELMAN: So is the panel recommending the indication for use statement to be changed, or the panel's recommendation somehow will get reflected somewhere else in

the labeling? I just want to be clear on --

DR. McCULLEY: You have a regulatory issue that I can't tell you how to deal with in how the study was done. But wherever that was stated, I think it needs to be not asterisked and put at the bottom of the page but imprint right after it that even though the study was initially done with this parameter, current practice is to have refractive stability defined as no greater than a half diopter change over the preceding year.

Is there agreement with that? Disagreement? Dr. Yaross?

DR. YAROSS: Marcia Yaross. I would just question is it the sponsor's job to say what is current medical practice if it deviates from how the study was done. I think that can cause some confusion.

DR. McCULLEY: Well, but I think it can also be harmful for the FDA to put its mark of approval on something that we currently don't consider adequate stability.

Dr. Jurkus?

DR. JURKUS: Jan Jurkus. I would have a real problem with the 1 diopter. Say, for example, if we had someone that might have been a quarter diopter myope and now was a 1.25 diopter myope six months later because of functional changes. They had the surgery done and they

might continue to become more myopic. So I think the half diopter is certainly more realistic.

DR. McCULLEY: So again, our recommendation is not to disadvantage sponsor, and I think both viewpoints or circumstances can be dealt with effectively.

Are there other comments from panel? Karen?

DR. BANDEEN-ROCHE: Karen Bandeen-Roche. This is purely a clarification. I'm just concerned that my comments in the record are very unclear as they stand. So just one sentence. The parameter for which I was computing a confidence bound is the proportion of subjects who can be expected to achieve some reversibility criterion, such as the proportion of subjects who can be expected to return to within 0.5 manifest refractive cylinder post-removal.

DR. McCULLEY: Okay. Other comments?

DR. MIDDLETON: I have two comments with respect to the patient booklets. Is it appropriate to make those now?

DR. McCULLEY: I think it's appropriate now.

DR. MIDDLETON: In the patient booklet under "Warnings," they list for near-sightedness that you should discuss with your doctor if your near-sightedness is changing, diabetic, et cetera. I think that they should indicate why, and they do so in the physician's booklet. They simply need to say the safety and effectiveness of the

ring has not been established in patients with these conditions. Rather than just listing those, don't leave a question in the consumer's mind. You should say why.

Then the second point, are you a good candidate for the KeraVision ring, I think that in the last bullet you're asking the patient to be informed as to the risks and the benefits as compared to all other available treatments. You should indicate what those treatments are, such as spectacles, contact lenses. Again, you do so in the physician's booklet. I don't think it's too much to ask or too much information to put there for the individual. In the very first bullet, the requirement is to be at least 21 years of age. You don't say to be the appropriate age and leave it to the individual to find out what that age is. You say 21. So by the same token, other available treatments, just list them. It's not a lot: spectacles, contact lenses, other surgical procedures. The same way you do in the physician's booklet I think you should do here.

Those are just two points that I would address.

DR. McCULLEY: Thank you.

Are there other comments from panel? Dr. Higginbotham.

DR. HIGGINBOTHAM: I'd like to follow Dr. Middleton's lead and suggest that in the patient booklet --

this is to humor me as well, I suppose -- on page 6, under "Warnings," I think we should explicitly state that you should discuss with your doctor if you have elevated pressure or a history of elevated pressure or a suspicion of glaucoma. I think as I read the booklet my understanding was that glaucoma was to be rolled into this overriding term called "disease." It may not come to the patient's mind if they don't actually see that word. So just a suggestion.

DR. McCULLEY: Other comments?

(No response.)

DR. McCULLEY: At this point I want to open the floor to another public hearing session. Anyone in the audience who would like to approach the podium other than the sponsor to make comments about the deliberations relative to this PMA specifically are invited to -- and it also can't be panel, Dr. Bullimore.

(Laughter.)

DR. McCULLEY: You'll lose more hair.

(Laughter.)

DR. McCULLEY: Please approach the podium at this time.

(No response.)

DR. McCULLEY: Seeing none, the open public hearing session is closed.

We now have the opportunity for five minutes of closing comments from sponsor.

DR. LEMP: Thank you. Dr. Lemp representing the sponsor.

First of all, the sponsor would like to thank the panel and the agency for a very careful evaluation of this device. We realize that we provided you with a lot of data, and it's difficult to analyze a lot of data, and we appreciate all the time and effort that you put in on this.

What I'd like to do is just make a couple of comments to a couple of the areas concerning comments that the panel had to try to clear things up.

The first comment relates to the vacuum time that Dr. Higginbotham brought up. It's important to recognize that the mean vacuum time on these procedures was 1.4 minutes, with a standard deviation of 0.43. So most of these procedures were about a minute and a half, just a little over a minute and a half.

A comment on your other question, this can be removed and reapplied, so it doesn't have to be continuous. So that's one point.

Another point that I would make has to do with the reversibility claim on this. I would just reiterate one thing that went by on a slide perhaps quickly and was not easy to assimilate all of these things.

If you use the most rigid criteria that we used for reversibility, which was return to within a half a diopter of the preop manifest spherical equivalent, a half a diopter of the preop cylinder, and one line plus or minus of visual acuity, 24 out of 27, or 89 percent met that criteria. That relates to some of the data points that Dr. Yaross brought up. If you use three-quarters of a diopter for the spherical equivalent and the cylinder, and one line, it's 100 percent of that N of 27.

The other points that I would bring up relate to endothelial cell density, and I think it's important to just clarify one or two points about that.

If you look at the eyes that had greater than 10 percent cell loss and you look at the six-month data, which we had for both the treated eye and the fellow eye, and that's as far out as we could get from the fellow eye because the fellow eye was eligible for implantation beyond that point, the number of patients who had greater than a 10 percent cell loss was 12 percent for the treated eyes and 9 percent for the fellow eyes at the six-month point. If you go out to 12 months, it was 14 percent for the treated eye -- that's one more eye than we found at the six-month data -- and four of those six eyes were the same.

Now, if you look at the data which we also presented, which was the paper by Trocme et al., which

looked at the longitudinal study of peripheral cell data in patients with PRK, which was the only study we could find that had any data on peripheral cell endothelial cell densities in a longitudinal study, they found a loss in the periphery of -6.9 percent, or 221 cells. If you look at our study, at the 10 o'clock position, which was the area of concern, we had at the same time a loss of -4.8 percent at the 10 o'clock position, which was 138 cells.

Now, in terms of the variability of this test that's already been alluded to, Dr. Edelhauser was a principal author on a paper that's just been published looking at endothelial cell density after LASIK. They were looking at central endothelial cell density, and even in the central endothelial cell density studies, there's a 10 percent variation, which relates to what Dr. McCulley was relating to earlier. That's 300 cells variation. So even in the central area, that seems to be the limit of the technology that we can do. That becomes considerably more problematic when you get to the periphery of the cornea, and particularly when you get to the periphery in a cornea that has its curvature changed in the area that you're looking at.

If you look at some of the specular photomicrographs, you can actually see the area where you can't see the cells as well, presumably when you start to

get that change, and it really adds to the question of the reproducibility. As Dr. Edelhauser has pointed out, you can't be sure you're coming back to the same area.

Now, in terms of your concern about longitudinal studies, I would say that the sponsor also agrees with some of your concerns. The real question is, is there any real cell loss here? We don't think there is. We think this is noise in the system, but it doesn't hurt to do some longitudinal studies. I'm not sure you're going to find anything, however, by doing longitudinal studies of the peripheral cornea, because we don't know that we're measuring anything there, that we have any reproducibility in this.

There have been a number of studies dating back quite a few years in terms of what happens when you do have real change in the periphery of the cornea secondary to injury, such as after surgery or when you create that injury, and you see it reflected in central endothelial cell counts because you get an equilibration of cells coming in, and we would think that it would make more sense if you're going to follow this that you follow the central cell counts because they would be much more reliable, more likely to have meaningful data than the peripheral cell counts because we have nothing to go on in terms of longitudinal studies for normals, and the methodology in

Cell appears to be inherently flawed.

So those are some of the comments we would make about those studies.

DR. McCULLEY: Mike, you have five minutes total. You're honing in on that.

DR. LEMP: Okay. Well, actually, that's about what I really wanted to say, except that as a sponsor I think all of us feel that we have provided reasonable assurance for the safety and effectiveness in all the ring sizes for the study. Thank you for your careful consideration.

DR. McCULLEY: Thank you, sponsor.

We now have five minutes for the FDA to make closing comments before we move towards voting, a motion.

(No response.)

DR. McCULLEY: Okay. You need to read the voting options.

MS. THORNTON: The panel voting options. The panel has a copy of these in their folder if they want to follow along.

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the

agency. The PMA must stand on its own merits, and the recommendations must be supported by safety and effectiveness data in the application, or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of use outweigh any probable risks. Effectiveness is defined as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses, and the conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows:

Approval. If you recommend approval, there are no conditions attached.

You can recommend approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or FDA staff. Prior to voting, all the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's response to the conditions of your approval recommendation you want; for example, FDA or panel. Panel follow-up is usually done

through homework assignments to the primary reviewers of the application or to other specified members of the panel. A formal discussion of the application at a future panel meeting is not usually held.

If you recommend post-approval requirements -- for example, post-approval follow-up studies or postmarket surveillance to be imposed as a condition of approval -- then your recommendation should address the following points: the purpose of the requirement, the number of subjects to be evaluated, and the reports required to be submitted.

The third option is not approvable. Of the five reasons the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations: the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling; reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the labeling; and based on a fair evaluation of all material facts in your discussions, you believe the proposed labeling to be false and misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask you

to identify the measures you think are necessary for the application to be placed in an approvable form. If FDA agrees with the panel's not approvable recommendation, we will send a "Not Approvable" letter. Please note: This is not a final agency action on the PMA. The applicant has the opportunity to amend the PMA to supply the requested information. The panel at a future meeting may review the amended application.

Please note that following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote. Traditionally, the consumer representative and the industry representative do not vote, and Dr. McCulley as chairperson votes only in the case of a tie.

Thank you, Dr. McCulley.

DR. McCULLEY: Dr. Sugar, would you like to make a motion?

DR. SUGAR: I'd like to move for approval with conditions, the conditions being the changes in the labeling that were discussed as we went through the eight questions. In addition, after approval, I would like to suggest that data continue to be accrued on endothelial cell counts as we discussed earlier also.

DR. McCULLEY: Is there a second?

DR. HIGGINBOTHAM: Second.

DR. McCULLEY: Is there further discussion?

DR. VAN METER: To specifically elaborate --

DR. McCULLEY: Dr. Van Meter.

DR. VAN METER: Dr. Van Meter. The endothelial cell counts you would do for the 0.35 millimeter implants only, and continue to follow those patients?

DR. SUGAR: No. What we discussed was all of the 0.35's and a selected group of the two others as a control.

DR. VAN METER: Okay, but that select group of others are the ones who have already had --

DR. SUGAR: All of this is patients who have already had surgery but will be followed subsequent to now.

DR. VAN METER: Thank you.

DR. McCULLEY: Dr. Grimmett?

DR. GRIMMETT: Just as a point of clarification, as long as we're thinking about a study on peripheral cell counts, as long as we're there, central cell counts too? Is that correct?

DR. SUGAR: The statement was endothelial cell counts presumably derived the same way they were previously in the study, which was three points -- 6, 10, and central.

DR. GRIMMETT: Thank you.

DR. McCULLEY: Other discussion? Dr. Bullimore.

DR. BULLIMORE: In addition to the Grimmett list of eight, I'm assuming that there are --

DR. McCULLEY: That was the eight questions, not the Grimmett eight. We're talking about the panel's response. I'm not going to try to reiterate all of those because I will leave something out.

DR. SUGAR: They also include the comments from Dr. Middleton on changes in the patient brochure.

DR. McCULLEY: Yes, the additional one. But we reached consensus on each point as we went through the eight questions. The various consensuses -- I guess that's a word -- that we agreed upon are part of the conditions.

Seeing no further requests for discussion, there's a call for the question.

All in favor of the motion, please signify by raising your right hand.

(Show of hands.)

DR. McCULLEY: I count 11 ayes.

All opposed?

(No response.)

DR. McCULLEY: Eleven is the total number of voting members. Therefore, the motion is unanimously recommended for approval, with conditions as stated.

Now we'll go around and each voting member will be asked to state the reasons for voting the way in which

you voted. We'll start with Karen, Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Karen Bandeen-Roche. I voted approvable with conditions because I believe that the sponsor has demonstrated the device to be safe and effective, subject to the labeling and other conditions we discussed.

DR. McCULLEY: Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. Based on my review, I believe the sponsor has shown reasonable safety and effectiveness with the labeling specifications that we discussed and the additional data that's needed on the endothelium.

DR. McCULLEY: Dr. Wang?

DR. WANG: Ming Wang. I think this is a reasonable and relatively safe option for refractive correction in the range that we discussed, and I recommend approval with conditions, with endothelial counts and other considerations included.

DR. VAN METER: Woody Van Meter. I voted approvable with conditions for the same reasons.

DR. McCULLEY: Dr. Matoba?

DR. MATOBA: Alice Matoba. I voted for approval for the same reasons.

DR. McCULLEY: Dr. Macsai?

DR. MACSAI: Dr. Macsai. I voted for

approvable with conditions basically because the perfect refractive surgical procedure does not exist. However, the KeraVision Intacts bring us closer to it. The Intacts appear to be reasonably effective and safe. There are concerns of continued endothelial cell loss. Some patients noted a decrease in their visual quality, with halos, double vision, and fluctuations in distance vision regardless of pupil size. However, as opposed to other refractive surgical procedures, the KeraVision Intacts are removable.

(Laughter.)

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: I voted approvable with conditions for similar reasons mentioned previously. Also, I'd like to state that I do thank the sponsors for giving us the data even though sometimes it was difficult to flush out. But they did give us good data to evaluate, which made our evaluations easier.

DR. HIGGINBOTHAM: Dr. Higginbotham. Based on the data presented both by the sponsor and FDA, and I must say that the data was well presented by both, and also the prospect of the long-term study on the cornea, I voted for approvable with conditions. Thank you.

DR. McCULLEY: Dr. Sugar?

DR. SUGAR: I voted for approvable with

conditions, and I pretty much stated my reasons. This appears to be a safe, effective, and reversible procedure.

(Laughter.)

DR. BULLIMORE: This is Dr. Bullimore. I voted for approvable with conditions for the same reasons.

DR. McCULLEY: Dr. Jurkus.

DR. JURKUS: Dr. Jurkus. I voted approvable with conditions for the same reasons.

DR. McCULLEY: Does FDA have any concluding remarks?

MS. THORNTON: I would just like to take the time to thank all of you for a very, very thorough preparation for this meeting. I know it was very difficult. There were a lot of volumes. It was quite heavy. It's in the interest of physical fitness that we send you these things.

(Laughter.)

MS. THORNTON: And to thank the sponsor for their time, and I appreciate your cooperation with this.

DR. McCULLEY: I'd like to thank the sponsor, the FDA, and the panel members for I think a well done session that did some good. Thank you.

We stand adjourned.

(Whereupon, at 3:35 p.m., the meeting was adjourned.)